USPTO Patent Full-Text and Image Database

10/613,914

Searching US Patent Collection...

Results of Search in US Patent Collection db for:
IN/(HORWITZ AND JEROME): 7 patents.
Hits 1 through 7 out of 7

Jump To

Refine Search in/(HORWITZ and JEROME)

PAT. NO.	Title
1 6,867,219	Antitumor agents
2 4,668,668	Compositions inhibiting murine MXT ductal carcinoma
3 4,636,496	Compositions inhibiting murine MXT ductal carcinoma
4 4,568,673	Compositions inhibiting murine MXT ductal carcinoma
5 4,496,555	Compounds and compositions for inhibiting estrogen sulfotransferase transferase activity, process and novel intermediates therein
6 4,266,048	Synthesis of analogs of 3'-phosphoadenosine 5'-phosphosulfate (PAPS)
7 4,169,011	Facile synthesis of 3'-phosphoadenosine 5'-phosphosulfate (PAPS)

USPTO Patent Full-Text and Image Database

Searching US Patent Collection...

Results of Search in US Patent Collection db for:
IN/(thomas AND corbett): 42 patents.
Hits 1 through 42 out of 42

Jump To

Refine Search in/(thomas and corbett)

	PAT. NO.	Title
1	7,032,666	Gravel pack crossover tool with check valve in the evacuation port
2	D518,722	Bottle
3	6,951,945	Heteroaromatic glucokinase activators
4	6,867,219	Antitumor agents
5	6,747,021	Cryptophycin compound
6	6,678,564	Bio-implant and method of making the same
7	6,610,846	Heteroaromatic glucokinase activators
8	6,573,296	Therapeutic quassinoid preparations with antineoplastic, antiviral, and herbistatic activity
9	6,528,543	Urea derivatives
10	6,320,050	Heteroaromatic glucokinase activators
11	6,241,443	Fastener with staged locking system
12	6,204,256	Acylated cyclodextrin derivatives
13	6,149,224	Break away trim panel assembly
14	6,087,762	Ultrasound transceiver and method for producing the same
15	6,013,626	Cryptophycins from synthesis
16	5,979,840	Apparatus for gripping a fluid carrying hose
17	5,965,493	Therapeutic Quassinoid preparations with antineoplastic, antiviral, and herbistatic activity
18	5,955,423	Cryptophycins
19	5,952,298	Cryptophycins
20	5,916,883	Acylated cyclodextrin derivatives
21	5,855,049	Method of producing an ultrasound transducer

22 5,849,748 Therapeutic quassinoid preparations with antineoplastic antiviral, and herbistatic activity
23 5,782,645 Percutaneous connector for multi-conductor electrical cables
24 5,683,117 Retainer clip for a connector
25 5,639,712 Therapeutic quassinoid preparations with antineoplastic, antiviral, and herbistatic activity
26 5,630,839 Multi-electrode cochlear implant and method of manufacturing the same
27 5,604,976 Method of making percutaneous connector for multi-conductor electrical cables
28 D365,410 Suspended lighting fixture
29 5,464,144 Surgical apparatus with indicator
30 D361,152 Hanging lamp
31 D361,151 Hanging lamp
32 5,380,749 Thioxanthenone antitumor agents
33 5,346,917 Thioxanthenone antitumor agents
34 5,087,069 Restraint system mounting
35 5,071,193 Cable mount for seat belt buckle
36 4,902,041 Bezel assembly for retractor
37 4,893,874 Free falling latch plate assembly
38 4,832,366 Adjustable shoulder belt
39 4,743,481 Molding process for articles having an irregular shaped internal passage
40 4,210,662 Side chain sulphoxide metabolites
41 4,138,403 Azabicycloheptanes
42 4,132,712 Antibacterial agents

Top View Cart
Home Quick Advanced Pat Num Help

USPTO Patent Full-Text and Image Database

Searching US Patent Collection...

10/613,914

Results of Search in US Patent Collection db for:
(CCL/544/354 AND quinolinyl): 68 patents.
Hits 1 through 50 out of 68

Final 18 Hits

Jump To

Refine Search ccl/544/354 and quinolinyl

	PAT. NO.	Title
1	6,943,170	N-cycloalkylglycines as HIV protease inhibitors
2	6,927,214	Non-peptide GLP-1 agonists
3	6,852,712	Quinoline and quinoxaline compounds which inhibit platelet-derived growth factor and/or p56lck tyrosine kinases
4	6,849,632	Heteroaryl alkyl piperazine derivatives
5	6,846,815	Quinoline and quinoxaline compounds which inhibit platelet-derived growth factor and/or p56lck tyrosine kinases
6	6,777,413	2-[1H]-quinolone and 2-[1H]-quinoxalone inhibitors of factor Xa
7	6,683,101	Bicyclic cyclohexylamines and their use as NMDA receptor antagonists
8	6,635,641	Amide compounds and pharmaceutical compositions for inhibiting protein kinases, and methods for their use
9	6,573,264	Heteroaryl alkyl piperazine derivatives
10	6,524,347	Quinoline and quinoxaline compounds which inhibit platelet-derived growth factor and/or p56lck tyrosine kinases
11	6,492,553	Methods for preparing N-[(aliphatic or aromatic)carbonyl)]-2-aminoaetamide compounds and for cyclizing such compounds
12	6,492,393	Compounds useful as anti-inflammatory agents
13	6,455,527	High affinity ligands for nociceptin receptor ORL-1
14	6,429,207	Metabotropic glutamate receptor antagonists and their use for treating central nervous system diseases
15	6,410,536	Quinoxalinones as serine protease inhibitors such as factor XA and thrombin
16	6,380,235	Benzimidazolones and analogues

17 6,376,490 Quinoxalinediones

18 6,372,750 Heterocyclic compounds, process for their preparation and pharmaceutical compounds containing them and their use in the treatment of diabetes and related diseases

19 6,288,082 Substituted 3-cyanoquinolines

20 6,268,366 Amide derivatives of substituted quinoxaline 2,3-diones as glutamate receptor antagonists

21 6,262,066 High affinity ligands for nociceptin receptor ORL-1

22 6,245,760 Quinoline and quinoxaline compounds which inhibit platelet-derived growth factor and/or p56lck tyrosine kinases

23 6,200,976 Antithrombotic quinoxazolines

24 6,191,134 Amide derivatives of substituted quinoxaline 2, 3-diones as glutamate receptor antagonists

25 6,180,632 Quinoline and quinoxaline compounds which inhibit platelet-derived growth factor and/or p56lck tyrosine kinases

26 6,166,041 2-heteroaryl and 2-heterocyclic benzoxazoles as PDE IV inhibitors for the treatment of asthma

27 6,159,978 Quinoline and quinoxaline compounds which inhibit platelet-derived growth factor and/or p56.sup.lck tyrosine kinases

28 6,080,743 2,3-dioxo-1,2,3,4-tetrahydro-quinoxalinyl derivatives

29 6,048,869 Tricyclic compounds

30 6,011,031 Azolidinediones useful for the treatment of diabetes, dyslipidemia and hypertension: process for their preparation and pharmaceutical compositions containing them

31 6,004,933 Cysteine protease inhibitors

32 5,985,884 Heterocyclic compounds, process for their preparation and pharmaceutical compositions containing them and their use in the treatment of diabetes and related diseases

33 RE36,256 Bis mono- and bicyclic aryl and heteroaryl compounds which inhibit EGF and/or PDGF receptor tyrosine kinase

34 5,789,408 Antiviral thiazoles

35 5,739,134 N-(3-hydroxy-4-piperidinyl)(dihydrobenzofuran, dihydro-2h-benzopyran, dihydrobenzodioxin, benzodioxole, dihydrobenzodioxepin, or tetrahydrobenzoxepin) carboxamide derivatives

36 5,679,680 .alpha.-substituted hydrazides having calpain inhibitory activity

37 5,622,962 5.alpha.-reductase inhibitors

38 5,622,961 5.alpha.-reductase inhibitors

39 5,578,724 Process for preparation of benzo[f]quinolinones

40 5,536,723 S-nitroso derivatives of hydrazinoacetic acids, 1-[(acylthio and (mercapto)-1-oxoalkyl]-1,2,34-Tetrahydroquinoline-2-carboxylic acids and alanyl prolines and isoquinolines

41 5,529,999 Antitumor compositions and methods of treatment

42 5,510,487 Retroviral protease inhibitors

43 5,480,883 Bis mono- and bicyclic aryl and heteroaryl compounds which inhibit EGF and/or PDGF receptor tyrosine kinase

44 5,409,930 Bis mono- and bicyclic aryl and heteroaryl compounds which inhibit EGF and/or PDGF receptor tyrosine kinase

45 5,346,902 Fungicidal diazinyl dioxime
46 5,324,839 Nitrogenous bicyclic derivatives substituted with benzyl
47 5,281,571 Herbicidal benzoxazinone- and benzothiazinone-substituted pyrazoles
48 5,250,690 Haloalkoxy anilide derivatives of 2-4(-heterocyclic oxyphenoxy)alkanoic or alkenoic acids and their use as herbicides
49 5,158,954 Methyl .alpha.-(2-substituted)pyrid-3-yl-.beta.-methoxy-acrylates, compositions containing them and their use as fungicides
50 5,147,878 Aminoalkoxyphenyl derivatives, process of preparation and compositions containing the same

---

Next List | Top | View Cart
Home | Quick | Advanced | Pat Num | Help

USPTO Patent Full-Text and Image Database

Searching US Patent Collection...

Results of Search in US Patent Collection db for:
((CCL/544/354 AND quinolinyl) AND amides): 25 patents.
Hits 1 through 25 out of 25

Jump To

Refine Search ccl/544/354 and quinolinyl and amides

	PAT. NO.	Title
1	6,852,712	Quinoline and quinoxaline compounds which inhibit platelet-derived growth factor and/or p56lck tyrosine kinases
2	6,846,815	Quinoline and quinoxaline compounds which inhibit platelet-derived growth factor and/or p56lck tyrosine kinases
3	6,777,413	2-[1H]-quinolone and 2-[1H]-quinoxalone inhibitors of factor Xa
4	6,635,641	Amide compounds and pharmaceutical compositions for inhibiting protein kinases, and methods for their use
5	6,524,347	Quinoline and quinoxaline compounds which inhibit platelet-derived growth factor and/or p56lck tyrosine kinases
6	6,492,553	Methods for preparing N-[(aliphatic or aromatic)carbonyl)]-2-aminoaetamide compounds and for cyclizing such compounds
7	6,429,207	Metabotropic glutamate receptor antagonists and their use for treating central nervous system diseases
8	6,410,536	Quinoxalinones as serine protease inhibitors such as factor XA and thrombin
9	6,372,750	Heterocyclic compounds, process for their preparation and pharmaceutical compounds containing them and their use in the treatment of diabetes and related diseases
10	6,288,082	Substituted 3-cyanoquinolines
11	6,268,366	Amide derivatives of substituted quinoxaline 2,3-diones as glutamate receptor antagonists
12	6,245,760	Quinoline and quinoxaline compounds which inhibit platelet-derived growth factor and/or p56lck tyrosine kinases
13	6,200,976	Antithrombotic quinoxazolines
14	6,191,134	Amide derivatives of substituted quinoxaline 2, 3-diones as glutamate receptor antagonists

15 6,180,632 Quinoline and quinoxaline compounds which inhibit platelet-derived growth factor and/or p56lck tyrosine kinases

16 6,159,978 T Quinoline and quinoxaline compounds which inhibit platelet-derived growth factor and/or p56.sup.lck tyrosine kinases

17 6,048,869 T Tricyclic compounds

18 6,011,031 T Azolidinediones useful for the treatment of diabetes, dyslipidemia and hypertension: process for their preparation and pharmaceutical compositions containing them

19 5,985,884 T Heterocyclic compounds, process for their preparation and pharmaceutical compositions containing them and their use in the treatment of diabetes and related diseases

20 5,739,134 T N-(3-hydroxy-4-piperidinyl)(dihydrobenzofuran, dihydro-2h-benzopyran, dihydrobenzodioxin, benzodioxole, dihydrobenzodioxepin, or tetrahydrobenzoxepin) carboxamide derivatives

21 5,536,723 T S-nitroso derivatives of hydrazinoacetic acids, 1-[(acylthio and (mercapto)-1-oxoalkyl]-1,2,34-Tetrahydroquinoline-2-carboxylic acids and alanyl prolines and isoquinolines

22 5,510,487 T Retroviral protease inhibitors

23 5,281,571 T Herbicidal benzoxazinone- and benzothiazinone-substituted pyrazoles

24 5,250,690 T Haloalkoxy anilide derivatives of 2-4(-heterocyclic oxyphenoxy)alkanoic or alkenoic acids and their use as herbicides

25 4,640,703 T 2-phenoxypropionic acid cyanamides as herbicides

---

Top View Cart

Home Quick Advanced Pat Num Help

USPTO Patent Full-Text and Image Database

Home | Quick | Advanced | Pat Num | Help

Bottom | View Cart

Searching US Patent Collection...

Results of Search in US Patent Collection db for:
((CCL/546/157 AND quinolinyl) AND amides): 43 patents.
Hits 1 through 43 out of 43

Jump To

Refine Search ccl/546/157 and quinolinyl and amides

	PAT. NO.	Title
1	7,019,139	Quinolinones and uses thereof
2	7,009,052	Sulfonamide derivatives
3	6,875,765	Arylsulfonamide ethers, and methods of use thereof
4	6,855,726	Quinolones as serine protease inhibitors
5	6,844,357	Substituted quinolin-2-one derivatives useful as antiproliferative agents
6	6,822,097	Compounds and methods of uses
7	6,800,760	Quinolinone derivatives
8	6,774,237	Quinolinone derivatives
9	6,713,462	Quinolinones and uses thereof
10	6,605,617	Quinolinone derivatives
11	6,579,887	Alkynyl-substituted quinolin-2-one derivatives useful as anticancer agents
12	6,495,564	Quinolin-2-one derivatives useful as anticancer agents
13	6,472,407	.alpha. and .beta.-amino acid hydroxyethylamino sulfonamides useful as retroviral protease inhibitors
14	6,420,387	Farnesyl protein transferase inhibiting (imidazol-5-yl) methyl-2-quinolinone derivatives
15	6,395,749	Carboxamide compounds, methods, and compositions for inhibiting PARP activity
16	6,329,389	Amine compounds, their production and use
17	6,294,552	Alkynyl-substituted quinolin-2-one derivatives useful as anticancer agents
18	6,258,824	Heteroaryl-substituted quinolin-2-one derivatives useful as anticancer agents
19	6,251,917	Benzamidoaldehydes and their use as cysteine protease inhibitors
20	6,248,739	Quinolinecarboxamides as antiviral agents
21	6,221,881	Nitrosated and nitrosylated phosphodiesterase inhibitor compounds, compositions and

their uses

22 6,174,901 Substituted pyridine and pyridazine compounds and methods of use

23 6,169,096 Farnesyl protein transferase inhibiting (imidazol-5-yl)methyl-2-quinolinone derivatives

24 6,150,377 Alkynyl-substituted quinolin-2-one derivatives useful as anticancer agents

25 6,037,350 Farnesyl protein transferase inhibiting (imidazol-5-yl)methyl-2-quionlinone derivatives

26 6,002,008 Substituted 3-cyano quinolines

27 5,968,952 Farnesyl transferase inhibiting 2-quinolone derivatives

28 5,708,174 Heterocyclic-esters or -amides used as 5-HT.sub.4 receptor antagonists

29 5,587,387 Heterocycle-substituted benzenemethanamine derivatives

30 5,480,997 Pyridine-substituted benzenemethanamine derivatives

31 5,414,088 2-bicyclobenzimidazoles, processes for their preparation and medicaments containing these compounds.

32 5,344,839 Sulfonamides as antifungal agents

33 5,250,690 Haloalkoxy anilide derivatives of 2-4(-heterocyclic oxyphenoxy)alkanoic or alkenoic acids and their use as herbicides

34 5,149,356 Herbicidal sulphonylaminocarbonyltriazolinones having substituents which are bonded via sulphur

35 5,142,060 Herbicidal substituted 4-sulphonylamino-2-azinyl-1,2,4-triazol-3-ones

36 5,094,683 Sulphonylaminocarbonyltriazolinones

37 5,037,841 1,3-disubstituted pyrrolidines

38 4,906,643 Substituted N-(3-hydroxy-4-piperidinyl)benzamides as gastrointestinal agents

39 4,889,864 Carbamoylimidazole derivatives and their use as fungicides

40 4,640,703 2-phenoxypropionic acid cyanamides as herbicides

41 4,558,130 Fluorogenic dihydroquinolone and dihydrocoumarin indicators for hydrogen peroxide

42 4,382,089 Antibacterial amide compounds, compositions thereof and methods of using them

43 4,236,912 Quinolinyloxyphenoxy and quinolyinylthiophenoxy alkanoic acids and derivatives thereof and methods of herbicidal use

---

Top | View Cart

Home | Quick | Advanced | Pat Num | Help

ACCESS DB # 188400

FOR OFFICIAL USE ONLY

RECEIVED

PLEASE PRINT CLEARLY

Scientific and Technical Information Center

SEARCH REQUEST FORM

(STIC)

Requester's Full Name: Sabiha Qazi Examiner #: 74141 Date: 5/2/06

Art Unit: 1616 Phone Number: 2-0622 Serial Number: 10/613,914

Location (Bldg/Room#): 4N45 (Mailbox #): 4C70 Results Format Preferred (circle): PAPER DISK

****

To ensure an efficient and quality search, please attach a copy of the cover sheet, claims, and abstract or fill out the following:

MG

Title of Invention: Therapeutic Amides

Inventors (please provide full names): Corbett et al.

Earliest Priority Date: 60/333,855 7/3/02

Search Topic:

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc., if known.

For Sequence Searches Only *Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.*

Please search for cls. 1, 21 & 49

Formula I, A = C

Specific compd in cl 49

Thanks

****

STAFF USE ONLY

Searcher: Sabiha Qazi

Searcher Phone #:

Searcher Location:

Date Searcher Picked Up: 5/10/06

Date Completed: 5/18/06

Searcher Prep & Review Time: 60

Online Time: 46

Type of Search

_____ NA Sequence (#)

_____ AA Sequence (#)

_____ Structure (#)

_____ Bibliographic

_____ Litigation

_____ Fulltext

_____ Other

Vendors and cost where applicable

✓ STN _____ Dialog

_____ Questel/Orbit _____ Lexis/Nexis

_____ Westlaw _____ WWW/Internet

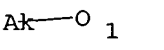
____ In-house sequence systems

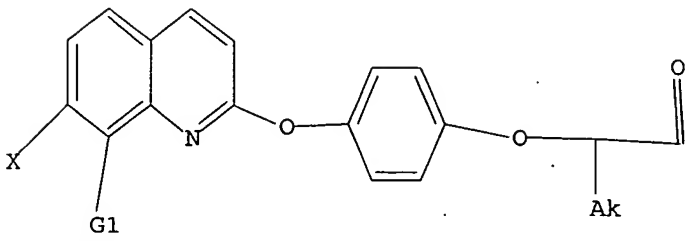
____ Commercial ____ Oligomer ____ Score/Length

____ Interference ____ SPDI ____ Encode/Transl

_____ Other (specify)

```
     FILE 'STNGUIDE' ENTERED AT 15:44:04 ON 11 MAY 2006
               D SCAN L4

     FILE 'CAPLUS' ENTERED AT 15:54:45 ON 11 MAY 2006
               D SCAN L4
L13          329 SEA ABB=ON  PLU=ON  (L6 OR L7 OR L8 OR L9 OR L10)
L14            6 SEA ABB=ON  PLU=ON  L13 AND ?AMID?/OBI
L15           44 SEA ABB=ON  PLU=ON  L13 AND ?AMID?/BI
L16           10 SEA ABB=ON  PLU=ON  L11 AND L15
L17           36 SEA ABB=ON  PLU=ON  (L12 OR L16)

     FILE 'REGISTRY' ENTERED AT 15:57:56 ON 11 MAY 2006
               D QUE L1
L18           32 SEA SSS FUL L1
               D SCAN

     FILE 'CAPLUS' ENTERED AT 15:59:53 ON 11 MAY 2006
L19            7 SEA ABB=ON  PLU=ON  L18

     FILE 'BEILSTEIN' ENTERED AT 16:00:12 ON 11 MAY 2006
L20            6 SEA SSS FUL L1
L21            6 SEA ABB=ON  PLU=ON  L20 NOT L18
L22              STRUCTURE UPLOADED
L23              QUE ABB=ON  PLU=ON  L22
L24            0 SEA SSS FUL L22

     FILE 'MARPAT' ENTERED AT 16:05:29 ON 11 MAY 2006
L25              STR L22
L26            0 SEA SSS SAM L25
               D QUE
L27            5 SEA SSS FUL L25
L28            3 SEA ABB=ON  PLU=ON  L27 NOT L19

     FILE 'CAPLUS' ENTERED AT 16:14:17 ON 11 MAY 2006

=> d que l19
L1               STR
```





G1 H,OH, [@1]

```
=> d his nofile

     (FILE 'HOME' ENTERED AT 15:33:15 ON 11 MAY 2006)

     FILE 'REGISTRY' ENTERED AT 15:33:20 ON 11 MAY 2006
L1             STRUCTURE UPLOADED
L2             QUE ABB=ON  PLU=ON  L1
L3           0 SEA SSS SAM L1

     FILE 'CAPLUS' ENTERED AT 15:33:45 ON 11 MAY 2006
               E US2003-613914/APPS
L4           2 SEA ABB=ON  PLU=ON  US2003-613914/AP
               SEL RN L4

     FILE 'REGISTRY' ENTERED AT 15:34:41 ON 11 MAY 2006
L5          70 SEA ABB=ON  PLU=ON  (347162-71-4/BI OR 347162-73-6/BI OR
                445041-69-0/BI OR 445041-70-3/BI OR 445041-74-7/BI OR 445041-75
                -8/BI OR 56-40-6/BI OR 613-77-4/BI OR 643752-97-0/BI OR
                643752-98-1/BI OR 643753-00-8/BI OR 643753-02-0/BI OR 643753-03
                -1/BI OR 643753-05-3/BI OR 643753-06-4/BI OR 643753-12-2/BI OR
                643753-13-3/BI OR 94050-90-5/BI OR 99455-15-9/BI OR 107-35-7/BI
                 OR 108-42-9/BI OR 108-44-1/BI OR 109-92-2/BI OR 148136-14-5/BI
                 OR 157434-99-6/BI OR 157435-10-4/BI OR 157542-89-7/BI OR
                157542-90-0/BI OR 157542-91-1/BI OR 157542-92-2/BI OR 160893-04
                -9/BI OR 160893-07-2/BI OR 22614-72-8/BI OR 23952-31-0/BI OR
                23981-22-8/BI OR 23981-26-2/BI OR 372-19-0/BI OR 4053-33-2/BI
                OR 4053-35-4/BI OR 4295-12-9/BI OR 445041-59-8/BI OR 445041-60-
                1/BI OR 445041-63-4/BI OR 445041-64-5/BI OR 445041-65-6/BI OR
                445041-68-9/BI OR 445041-72-5/BI OR 445041-73-6/BI OR 455955-27
                -8/BI OR 49609-15-6/BI OR 536-90-3/BI OR 591-19-5/BI OR
                59412-12-3/BI OR 643752-95-8/BI OR 643753-11-1/BI OR 646505-47-
                7/BI OR 646505-48-8/BI OR 646505-49-9/BI OR 646505-50-2/BI OR
                646505-51-3/BI OR 647026-59-3/BI OR 647026-61-7/BI OR 67648-61-
                7/BI OR 7347-25-3/BI OR 79-37-8/BI OR 99455-13-7/BI OR
                99465-09-5/BI OR 99465-10-8/BI OR 99465-18-6/BI OR 99471-66-6/B
                I)

     FILE 'CAPLUS' ENTERED AT 15:40:02 ON 11 MAY 2006
               E HORWITZ J/AU
L6         163 SEA ABB=ON  PLU=ON  ("HORWITZ J"/AU OR "HORWITZ J P"/AU OR
                "HORWITZ JEROME"/AU OR "HORWITZ JEROME P"/AU)
               E CORBETT T/AU
L7         155 SEA ABB=ON  PLU=ON  ("CORBETT T"/AU OR "CORBETT T H"/AU OR
                "CORBETT THOMAS"/AU OR "CORBETT THOMAS H"/AU OR "CORBETT
                THOMAS HUGHES"/AU)
               E PALOMINO E/AU
L8          31 SEA ABB=ON  PLU=ON  ("PALOMINO E"/AU OR "PALOMINO EDUARDO"/AU)

               E POLIN L/AU
L9          45 SEA ABB=ON  PLU=ON  ("POLIN L"/AU OR "POLIN LISA"/AU OR "POLIN
                LISA A"/AU OR "POLIN LISA ANNE"/AU OR "POLIN LISA MARIE"/AU)
               E HAZELDINE S/AU
L10         12 SEA ABB=ON  PLU=ON  ("HAZELDINE S"/AU OR "HAZELDINE STEWART
                T"/AU OR "HAZELDINE STUART"/AU OR "HAZELDINE STUART T"/AU OR
                "HAZELDINE STUART THOMAS"/AU)
L11         46 SEA ABB=ON  PLU=ON  (L6 AND (L7 OR L8 OR L9 OR L10)) OR (L7
                AND (L8 OR L9 OR L10)) OR (L8 AND (L9 OR L10)) OR (L9 AND L10)
L12         33 SEA ABB=ON  PLU=ON  L11 NOT (PY>2002 OR AY>2002 OR PRY>2002)
```

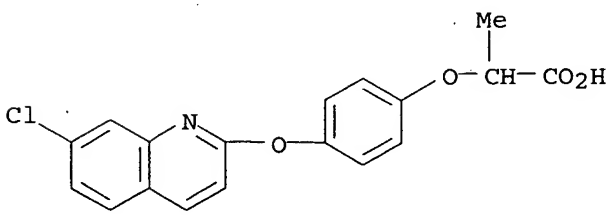
Structure attributes must be viewed using STN Express query preparation.
L18 32 SEA FILE=REGISTRY SSS FUL L1
L19 7 SEA FILE=CAPLUS ABB=ON PLU=ON L18

=> d ibib abs hitstr l19 tot

L19 ANSWER 1 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2006:156957 CAPLUS
TITLE: Synthesis and biological evaluation of conformationally constrained analogs of the antitumor agents XK469 and SH80. Part 5
AUTHOR(S): Hazeldine, Stuart T.; Polin, Lisa; Kushner, Juiwanna; White, Kathryn; Corbett, Thomas H.; Horwitz, Jerome P.
CORPORATE SOURCE: Department of Internal Medicine, Division of Hematology and Oncology, Wayne State University School of Medicine, Barbara Ann Karmanos Cancer Institute, Detroit, MI, USA
SOURCE: Bioorganic & Medicinal Chemistry (2006), 14(7), 2462-2467
CODEN: BMECEP; ISSN: 0968-0896
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

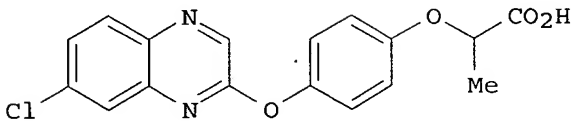
AB Conformational restriction of bioactive mols. offers the possibility of generating structures of increased potency. To this end, a synthesis has been achieved of (R,S)-2-[(8-chlorobenzofurano[2,3-b]quinolinyl)oxy]propionic acid (12a), a highly rigidified, polycyclic analog of 2-{4-[(7-chloro-2-quinoxalinyl)oxy]phenoxy}propionic acid (2a, XK469). Efforts to effect the same synthesis of the corresponding 8-bromo-derivative led to a mixture of intermediate, 8-chloro (9a), and 8-bromo-2-hydroxybenzofurano[2,3-b]quinoline (9b), generated by halogen-exchange, via an aromatic SRN 1(ARN 1) reaction of precursor, 8b, with pyridine hydrochloride. The presumption that conformational restriction of 1b-12a might enhance the antitumor potency of the latter has not been sustained. In fact, 12a proved to be significantly less active than 1b. However, it is apparent that virtually all of the spatial and steric properties of 12a, necessary for improved activity, including the disposition of the 2-oxypropionic acid side chain remain to be identified.

IT **445041-69-0**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antitumor activity of conformationally constrained benzofuranoquinolines)
RN 445041-69-0 CAPLUS
CN Propanoic acid, 2-[4-[(7-chloro-2-quinolinyl)oxy]phenoxy]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 2 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:69131 CAPLUS
DOCUMENT NUMBER: 142:298019
TITLE: Part 3: Synthesis and biological evaluation of some analogs of the antitumor agents, 2-{4-[(7-chloro-2-quinoxalinyl)oxy]phenoxy}propionic acid, and 2-{4-[(7-bromo-2-quinolinyl)oxy]phenoxy}propionic acid
AUTHOR(S): Hazeldine, Stuart T.; Polin, Lisa; Kushner, Juiwanna; White, Kathryn; Corbett, Thomas H.; Biehl, Jason; Horwitz, Jerome P.
CORPORATE SOURCE: Barbara Ann Karmanos Cancer Institute, Department of Internal Medicine, Division of Hematology and Oncology, School of Medicine, Wayne State University, Detroit, MI, USA
SOURCE: Bioorganic & Medicinal Chemistry (2005), 13(4), 1069-1081
CODEN: BMECEP; ISSN: 0968-0896
PUBLISHER: Elsevier Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 142:298019
GI



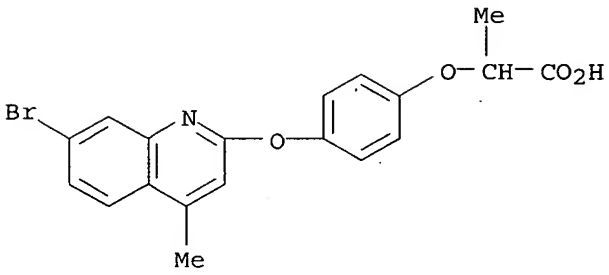
I

AB 2-{4-[(7-Chloro-2-quinoxalinyl)oxy]phenoxy}propionic acid (I; XK469) and 2-{4-[(7-bromo-2-quinolinyl)oxy]phenoxy}propionic Acid (SH80) are highly and broadly active antitumor agents to have been developed. However, the mechanism(s) of action of these agents remain to be elucidated, which led to continued endeavor to delineate a pharmacophoric pattern, from which a putative target might be deduced. Herein, addnl. evidence that intact quinoxaline and quinoline rings in XK469 and SH80, resp., are fundamental to the activities of these structures against transplanted tumors in mice, is reported. The consequence of further modification of the heterocyclic ring system in XK469 and SH80, leading to [1,8]naphthyridine; pyrrolo[1,2-a]; imidazo[1,2-a]; and imidazo[1,5-a] derivs., all deprive the parent structures of antitumor activity. Introduction of CH3, CF3, CH3O, CO2H, or C6H5 substituents at C4 of the quinoline ring of SH80 led to weakly active antitumor agents. Similarly, the phenanthridine analog of SH80 manifested only modest cytotoxicity. Lastly, XK469 and SH80 were both significantly more active than the corresponding regioisomeric structures, 2-4-{[(7-halo-4-quinolinyl)oxy]phenoxy}propionic acids.

IT **847900-62-3P**
RL: PAC (Pharmacological activity); PEP (Physical, engineering or chemical process); PYP (Physical process); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); PROC (Process)
(preparation and antitumor activity of [(chloroquinoxalinyloxy)phenoxy]- and [(bromoquinolinyloxy)phenoxy]propionic acids using etherification as the key step)

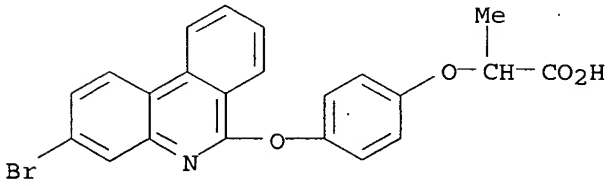
RN 847900-62-3 CAPLUS

CN Propanoic acid, 2-[4-[(7-bromo-4-methyl-2-quinolinyl)oxy]phenoxy]- (9CI) (CA INDEX NAME)

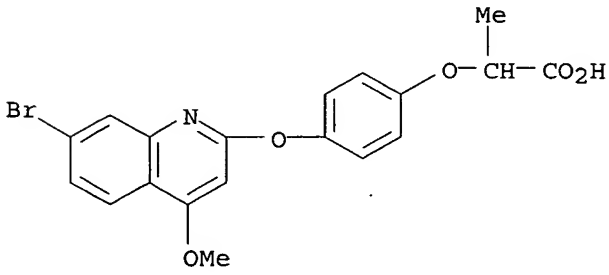


IT **847900-60-1P 847900-63-4P 847900-76-9P 847900-78-1P 847900-81-6P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation and antitumor activity of [(chloroquinoxalinyloxy)phenoxy]- and [(bromoquinolinyloxy)phenoxy]propionic acids using etherification as the key step)

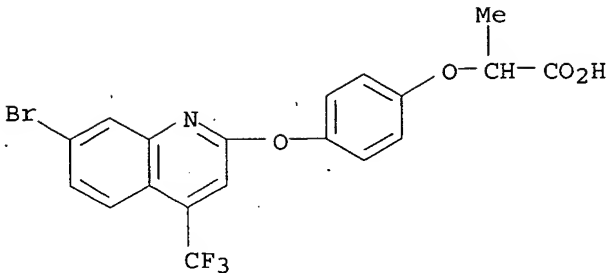
RN 847900-60-1 CAPLUS
CN Propanoic acid, 2-[4-[(3-bromo-6-phenanthridinyl)oxy]phenoxy]- (9CI) (CA INDEX NAME)



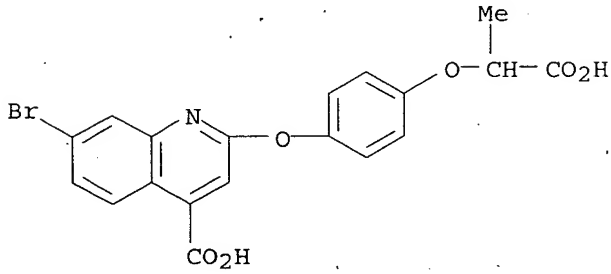
RN 847900-63-4 CAPLUS
CN Propanoic acid, 2-[4-[(7-bromo-4-methoxy-2-quinolinyl)oxy]phenoxy]- (9CI) (CA INDEX NAME)



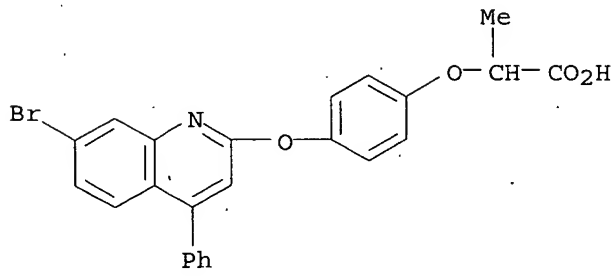
RN 847900-76-9 CAPLUS
CN Propanoic acid, 2-[4-[[7-bromo-4-(trifluoromethyl)-2-quinolinyl]oxy]phenoxy]- (9CI) (CA INDEX NAME)



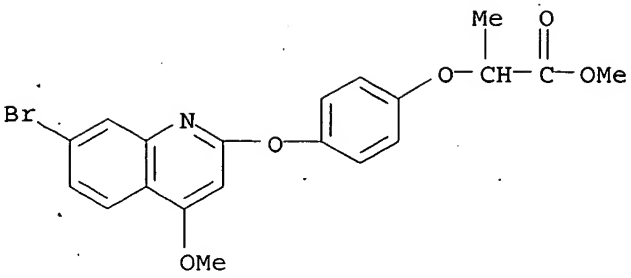
RN 847900-78-1 CAPLUS
CN 4-Quinolinecarboxylic acid, 7-bromo-2-[4-(1-carboxyethoxy)phenoxy]- (9CI) (CA INDEX NAME)



RN 847900-81-6 CAPLUS
CN Propanoic acid, 2-[4-[(7-bromo-4-phenyl-2-quinolinyl)oxy]phenoxy]- (9CI) (CA INDEX NAME)

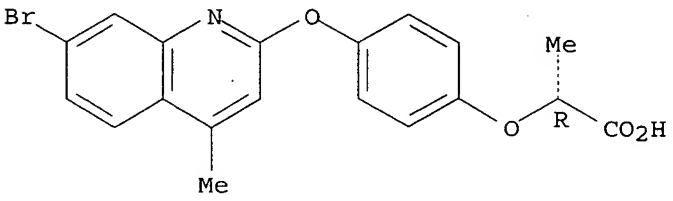


IT **847900-69-0P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and antitumor activity of [(chloroquinoxalinyloxy)phenoxy]- and [(bromoquinolinyloxy)phenoxy]propionic acids using etherification as the key step)
RN 847900-69-0 CAPLUS
CN Propanoic acid, 2-[4-[(7-bromo-4-methoxy-2-quinolinyl)oxy]phenoxy]-, methyl ester (9CI) (CA INDEX NAME)



IT **847900-64-5P**
RL: PAC (Pharmacological activity); PUR (Purification or recovery); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(stereoselective preparation and antitumor activity of [(chloroquinoxalinyloxy)phenoxy]- and [(bromoquinolinyloxy)phenoxy]propionic acids using etherification and HPLC separation as the key steps)
RN 847900-64-5 CAPLUS
CN Propanoic acid, 2-[4-[(7-bromo-4-methyl-2-quinolinyl)oxy]phenoxy]-, (2R)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:41446 CAPLUS
DOCUMENT NUMBER: 140:111288
TITLE: Preparation of 2-[4-[(7-halo-2-quinolinyl)oxy]phenoxy]propionic acid derivatives and quinoxalinyl analogs as antineoplastic agents
INVENTOR(S): Horwitz, Jerome P.; Corbett, Thomas H.; Palomino, Eduardo; Polin, Lisa; Hazeldine, Stuart T.
PATENT ASSIGNEE(S): Wayne State University, USA
SOURCE: PCT Int. Appl., 67 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

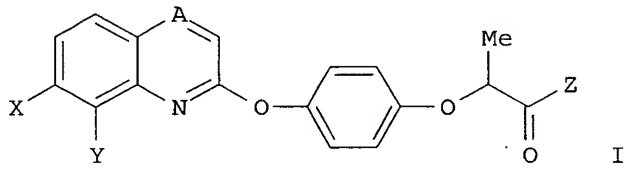
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004005260	A1	20040115	WO 2003-US21062	20030703

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM,

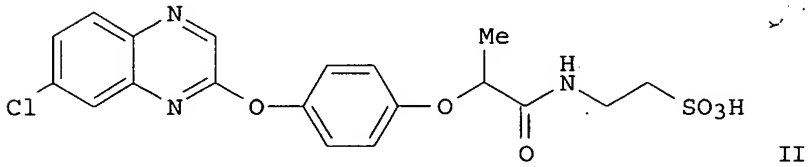
PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN,
TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,
BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

CA 2491612	AA	20040115	CA 2003-2491612	20030703
AU 2003249704	A1	20040123	AU 2003-249704	20030703
US 2004132618	A1	20040708	US 2003-613914	20030703
BR 2003011491	A	20050426	BR 2003-11491	20030703
EP 1539699	A1	20050615	EP 2003-763213	20030703
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
JP 2005532397	T2	20051027	JP 2004-519888	20030703
NO 2005000573	A	20050202	NO 2005-573	20050202
PRIORITY APPLN. INFO.:			US 2002-393858P	P 20020703
			WO 2003-US21062	W 20030703

OTHER SOURCE(S): MARPAT 140:111288
GI



I



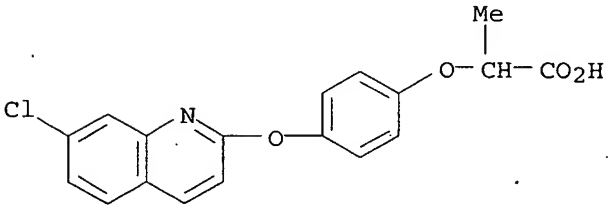
II

AB Title compds. I [wherein A = CH or N; X = F, Cl, or Br; Y = H, OH, or alkoxy; Z = an amino acid or heterocycle; and pharmaceutically acceptable salts thereof] were prepared and tested in vivo as antitumor agents. Preferred compds. of the invention and their pharmaceutical compns. are more potent and less toxic than the known antitumor agent, 2-[4-[(7-chloro-2-quinoxalinyl)oxy]phenoxy]propanoic acid sodium salt (XK 469), and have a different metabolic profile than XK 469. For example, XK 469 was refluxed with SOCl2 for 1 h and the resulting acid chloride treated with β-aminoethylsulfonate (taurine) and 1M NaOH in THF to give II•Na (74%). Chiral HPLC separation afforded the enantiomers. (R)-II•Na was well tolerated in mice at a total dose of 1610 mg/kg i.v. and was highly active (T/C = 0%, log cell kill = 4.2) against early stage murine mammary adenocarcinoma 16/C. No adverse symptoms or cures were noted post injection.

IT **445041-69-0P**
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or

reagent); USES (Uses)
(antitumor agent; preparation of [[(haloquinolinyl)oxy]phenoxy]propionic acid derivs. and quinoxalinyl analogs as antineoplastic agents)

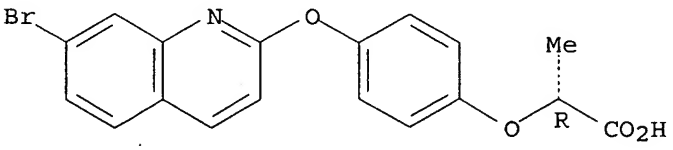
RN 445041-69-0 CAPLUS
CN Propanoic acid, 2-[4-[(7-chloro-2-quinolinyl)oxy]phenoxy]- (9CI) (CA INDEX NAME)



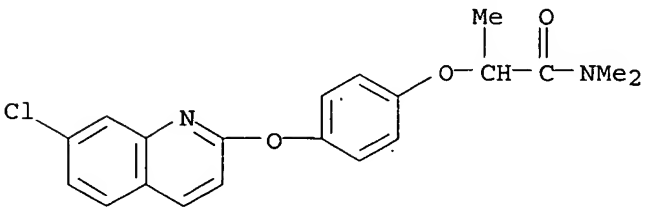
IT **445041-75-8P**, (R)-2-[4-[(7-Bromo-2-quinolinyl)oxy]phenoxy]propionic acid **643753-00-8P**, 2-[4-[(7-Chloro-2-quinolinyl)oxy]phenoxy]-N,N-dimethylpropionamide **643753-13-3P 646505-48-8P 646505-49-9P**, (R)-[[2-[4-[(7-Bromoquinolin-2-yl)oxy]phenoxy]propionyl]amino]acetic acid **646505-51-3P**
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(antitumor agent; preparation of [[(haloquinolinyl)oxy]phenoxy]propionic acid derivs. and quinoxalinyl analogs as antineoplastic agents)

RN 445041-75-8 CAPLUS
CN Propanoic acid, 2-[4-[(7-bromo-2-quinolinyl)oxy]phenoxy]-, (2R)- (9CI) (CA INDEX NAME)

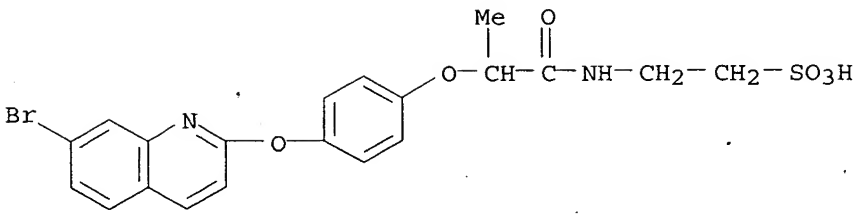
Absolute stereochemistry. Rotation (+).



RN 643753-00-8 CAPLUS
CN Propanamide, 2-[4-[(7-chloro-2-quinolinyl)oxy]phenoxy]-N,N-dimethyl- (9CI) (CA INDEX NAME)



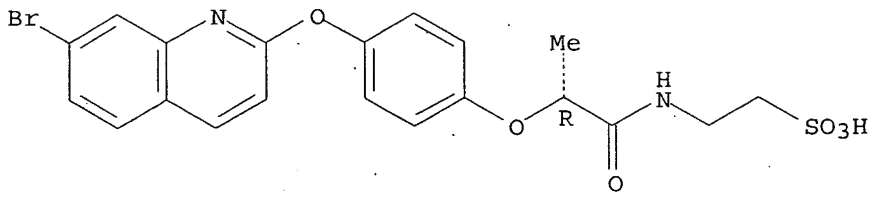
RN 643753-13-3 CAPLUS
CN Ethanesulfonic acid, 2-[[2-[4-[(7-bromo-2-quinolinyl)oxy]phenoxy]-1-oxopropyl]amino]-, monosodium salt (9CI) (CA INDEX NAME)



● Na

RN 646505-48-8 CAPLUS
CN Ethanesulfonic acid, 2-[[(2R)-2-[4-[(7-bromo-2-quinolinyl)oxy]phenoxy]-1-oxopropyl]amino]-, monosodium salt (9CI) (CA INDEX NAME)

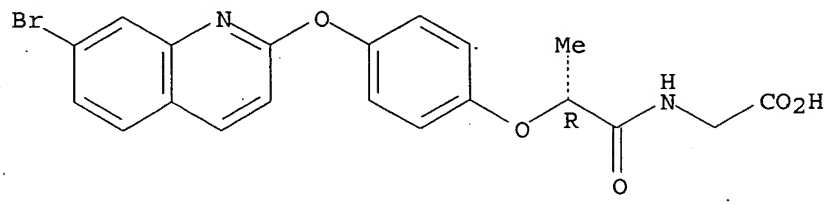
Absolute stereochemistry. Rotation (+).



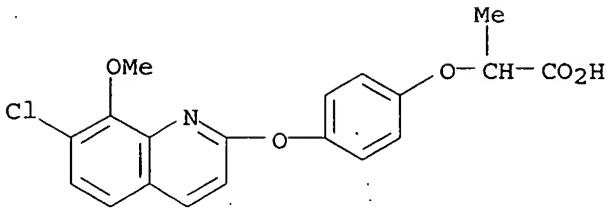
● Na

RN 646505-49-9 CAPLUS
CN Glycine, N-[(2R)-2-[4-[(7-bromo-2-quinolinyl)oxy]phenoxy]-1-oxopropyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



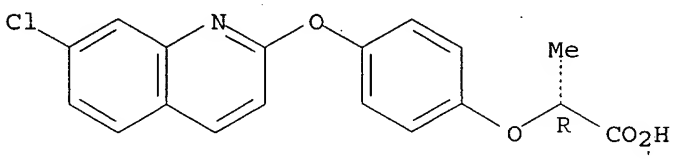
RN 646505-51-3 CAPLUS
CN Propanoic acid, 2-[4-[(7-chloro-8-methoxy-2-quinolinyl)oxy]phenoxy]- (9CI) (CA INDEX NAME)



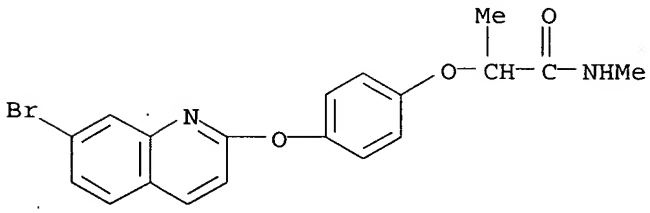
IT **445041-74-7P**, (R)-2-[4-[(7-Chloro-2-quinolinyl)oxy]phenoxy]propion ic acid **643752-98-1P**, 2-[4-[(7-Bromo-2-quinolinyl)oxy]phenoxy]-N-methylpropionamide **643753-03-1P 643753-05-3P**, [[2-[4-[(7-Bromoquinolin-2-yl)oxy]phenoxy]propionyl]amino]acetic acid **647026-61-7P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(antitumor agent; preparation of [[(haloquinolinyl)oxy]phenoxy]propionic acid derivs. and quinoxalinyl analogs as antineoplastic agents)

RN 445041-74-7 CAPLUS
CN Propanoic acid, 2-[4-[(7-chloro-2-quinolinyl)oxy]phenoxy]-, (2R)- (9CI) (CA INDEX NAME)

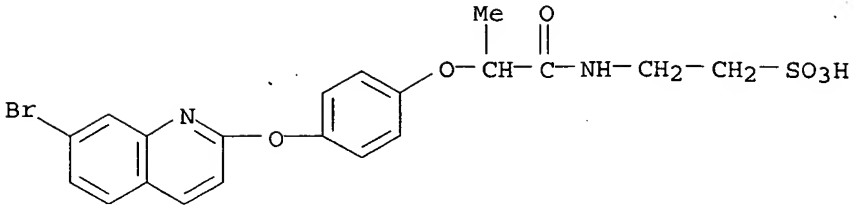
Absolute stereochemistry. Rotation (+).



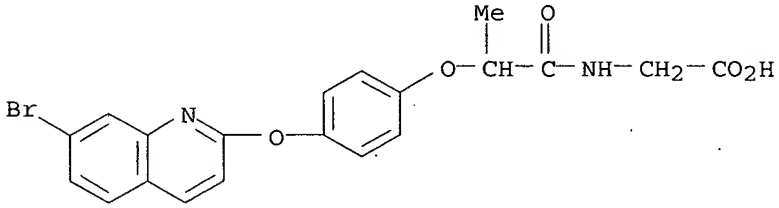
RN 643752-98-1 CAPLUS
CN Propanamide, 2-[4-[(7-bromo-2-quinolinyl)oxy]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)



RN 643753-03-1 CAPLUS
CN Ethanesulfonic acid, 2-[[2-[4-[(7-bromo-2-quinolinyl)oxy]phenoxy]-1-oxopropyl]amino]- (9CI) (CA INDEX NAME)

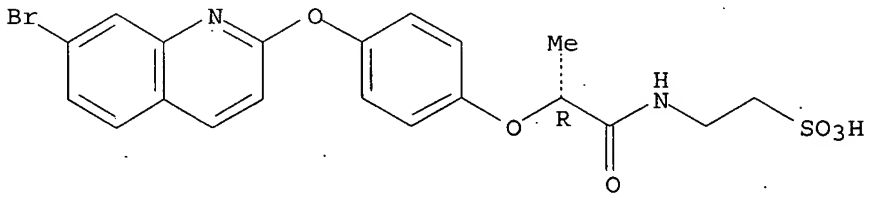


RN 643753-05-3 CAPLUS
CN Glycine, N-[2-[4-[(7-bromo-2-quinolinyl)oxy]phenoxy]-1-oxopropyl]- (9CI) (CA INDEX NAME)

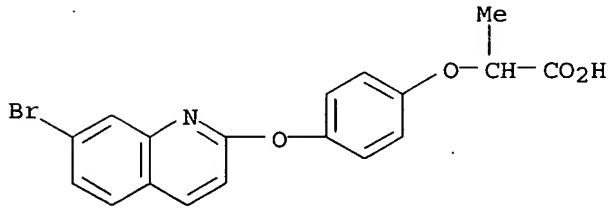


RN 647026-61-7 CAPLUS
CN Ethanesulfonic acid, 2-[[(2R)-2-[4-[(7-bromo-2-quinolinyl)oxy]phenoxy]-1-oxopropyl]amino]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



IT **445041-70-3**, 2-[4-[(7-Bromo-2-quinolinyl)oxy]phenoxy]propionic acid
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of [[(haloquinolinyl)oxy]phenoxy]propionic acid derivs. and quinoxalinyl analogs as antineoplastic agents)
RN 445041-70-3 CAPLUS
CN Propanoic acid, 2-[4-[(7-bromo-2-quinolinyl)oxy]phenoxy]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 4 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:41220 CAPLUS
DOCUMENT NUMBER: 140:99632
TITLE: Preparation of therapeutic amides as antitumor agents
INVENTOR(S): Horwitz, Jerome P.; Corbett, Thomas H.; Palomino, Eduardo; Polin, Lisa; Hazeldine, Stuart T.
PATENT ASSIGNEE(S): Wayne State University, USA
SOURCE: PCT Int. Appl., 52 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

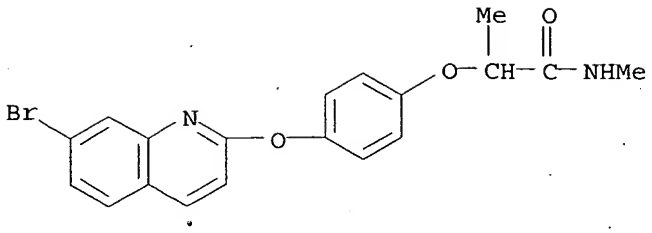
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004004651	A2	20040115	WO 2003-US21126	20030703
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004132618	A1	20040708	US 2003-613914	20030703
PRIORITY APPLN. INFO.:			US 2002-393858P P	20020703

OTHER SOURCE(S): MARPAT 140:99632

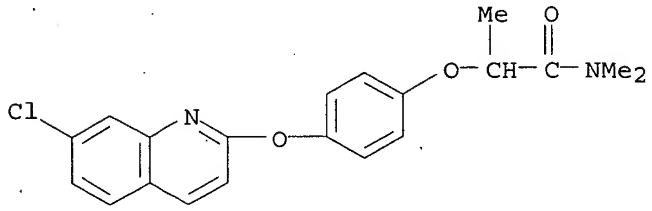
AB Amides, e.g., 2-{4-((7-bromo-2-quinolinyl)oxy)phenoxy}propionmethylamide, {2-{4-(7-bromoquinolin-2-yloxy)phenoxy}propionylamino}acetic acid, or 4-(7-chloro-2-quinolinyl)oxyphenoxypropionylaminoethanesulfonic acid,are prepared for use as effective antitumor agents. The invention also provides pharmaceutical compns. comprising the above compound, intermediates useful for preparing the compds., and methods for administering the compds. to a mammal. Thus, sodium (2-(4-(7-chloro-2-quinolinyl)oxy)phenoxy)propionylam inoethanesulfonate was prepared in a series of steps by starting from Et vinyl ether with oxalyl chloride followed by treatment with substituted anilines cyclization, and subsequent treatment with 2-(4-hydroxyphenoxy)propionic acid. Tablets contained the above compound 100.0, lactose 77.5, Povidone 15.0, Croscarmellose sodium 12.0, microcryst. cellulose 92.5, and Mg stearate 3.0 mg/tablet. The compound had activity against adenocarcinoma.

IT **643752-98-1P 643753-00-8P 643753-03-1P**
643753-05-3P 643753-13-3P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of therapeutic amides as antitumor agents)

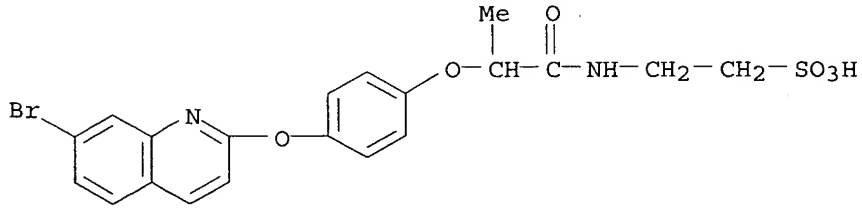
RN 643752-98-1 CAPLUS
CN Propanamide, 2-[4-[(7-bromo-2-quinolinyl)oxy]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)



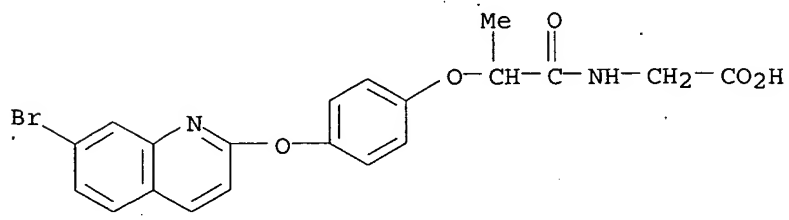
RN 643753-00-8 CAPLUS
CN Propanamide, 2-[4-[(7-chloro-2-quinolinyl)oxy]phenoxy]-N,N-dimethyl- (9CI) (CA INDEX NAME)



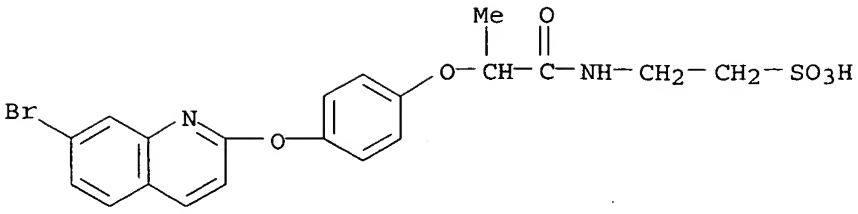
RN 643753-03-1 CAPLUS
CN Ethanesulfonic acid, 2-[[2-[4-[(7-bromo-2-quinolinyl)oxy]phenoxy]-1-oxopropyl]amino]- (9CI) (CA INDEX NAME)



RN 643753-05-3 CAPLUS
CN Glycine, N-[2-[4-[(7-bromo-2-quinolinyl)oxy]phenoxy]-1-oxopropyl]- (9CI) (CA INDEX NAME)



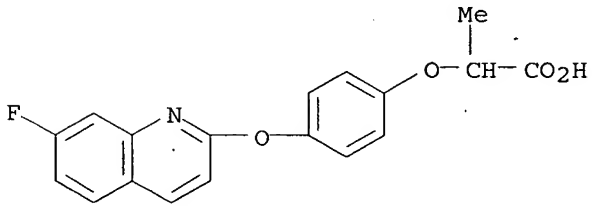
RN 643753-13-3 CAPLUS
CN Ethanesulfonic acid, 2-[[2-[4-[(7-bromo-2-quinolinyl)oxy]phenoxy]-1-oxopropyl]amino]-, monosodium salt (9CI) (CA INDEX NAME)



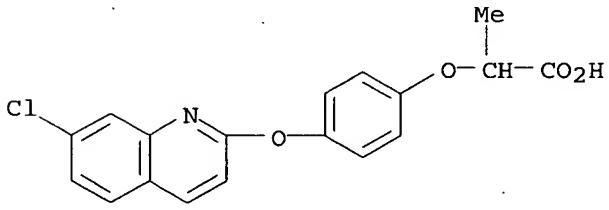
● Na

IT **445041-68-9P 445041-69-0P 445041-70-3P**
445041-74-7P 445041-75-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of therapeutic amides as antitumor agents)

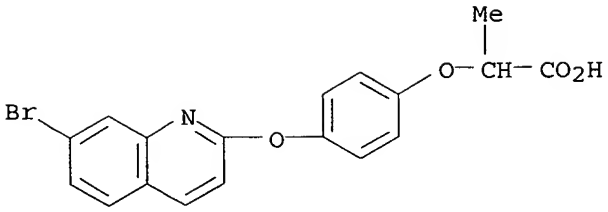
RN 445041-68-9 CAPLUS
CN Propanoic acid, 2-[4-[(7-fluoro-2-quinolinyl)oxy]phenoxy]- (9CI) (CA INDEX NAME)



RN 445041-69-0 CAPLUS
CN Propanoic acid, 2-[4-[(7-chloro-2-quinolinyl)oxy]phenoxy]- (9CI) (CA INDEX NAME)

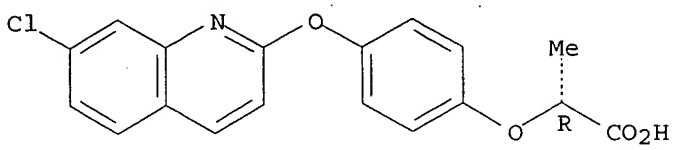


RN 445041-70-3 CAPLUS
CN Propanoic acid, 2-[4-[(7-bromo-2-quinolinyl)oxy]phenoxy]- (9CI) (CA INDEX NAME)



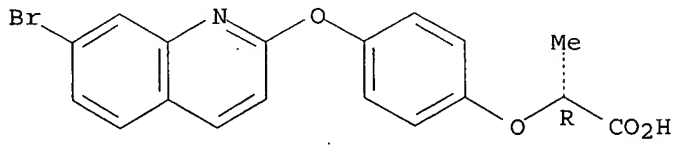
RN 445041-74-7 CAPLUS
CN Propanoic acid, 2-[4-[(7-chloro-2-quinolinyl)oxy]phenoxy]-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 445041-75-8 CAPLUS
CN Propanoic acid, 2-[4-[(7-bromo-2-quinolinyl)oxy]phenoxy]-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L19 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:117802 CAPLUS
DOCUMENT NUMBER: 138:153448
TITLE: Preparation of quinoline derivatives and there use as antitumor agents
INVENTOR(S): Horwitz, Jerome P.; Hazeldine, Stewart T.; Corbett, Thomas H.; Polin, Lisa
PATENT ASSIGNEE(S): Wayne State University, USA
SOURCE: PCT Int. Appl., 44 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

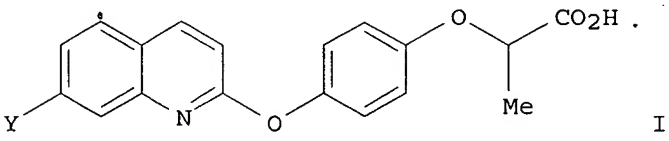
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003011832	A1	20030213	WO 2002-US24442	20020731

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,

PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

CA 2456173	AA	20030213	CA 2002-2456173	20020731
US 2003144321	A1	20030731	US 2002-210781	20020731
US 6867219	B2	20050315		
EP 1412332	A1	20040428	EP 2002-752656	20020731
EP 1412332	B1	20050119		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
BR 2002011629	A	20040824	BR 2002-11629	20020731
JP 2004538314	T2	20041224	JP 2003-517024	20020731
AT 287397	E	20050215	AT 2002-752656	20020731
PT 1412332	T	20050630	PT 2002-752656	20020731
ES 2236548	T3	20050716	ES 2002-2752656	20020731
NO 2004000382	A	20040326	NO 2004-382	20040128
ZA 2004001185	A	20041021	ZA 2004-1185	20040213
US 2005159447	A1	20050721	US 2004-9457	20041210
PRIORITY APPLN. INFO.:			US 2001-309144P	P 20010731
			US 2002-210781	A1 20020731
			WO 2002-US24442	W 20020731

OTHER SOURCE(S): MARPAT 138:153448
GI



I

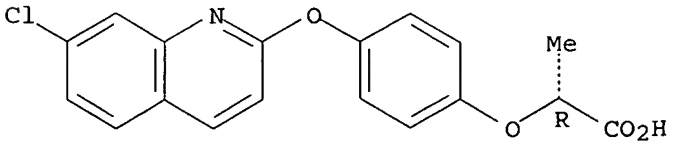
AB Title compds. I [Y = F, Cl, Br, Me, MeO or a pharmaceutically acceptable salt thereof] are prepared For instance, 2-[4-(7-chloroquinolin-2-yloxy)phenoxy]propanoic acid (II) is prepared from the corresponding phenol and 2,7-dichloroquinoline. R-II exhibited efficacy against early stage mammary cancer (Mam-17/Adr; mice) and showed none of the neuromuscular toxicity that occurred with rac-II.

IT **445041-74-7P**
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of quinoline derivs. and there use as antitumor agents)

RN 445041-74-7 CAPLUS

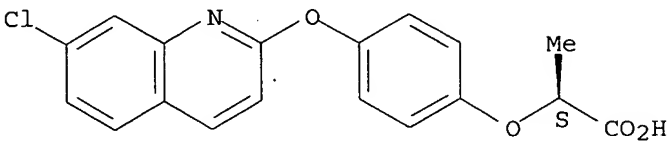
CN Propanoic acid, 2-[4-[(7-chloro-2-quinolinyl)oxy]phenoxy]-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



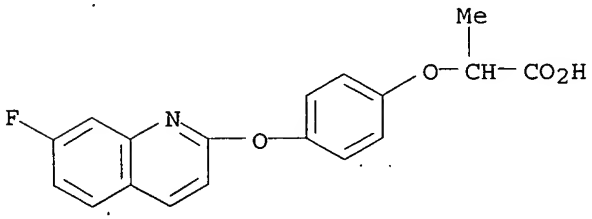
IT **496802-57-4**
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of quinoline derivs. and there use as antitumor agents)
RN 496802-57-4 CAPLUS
CN Propanoic acid, 2-[4-[(7-chloro-2-quinolinyl)oxy]phenoxy]-, sodium salt, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

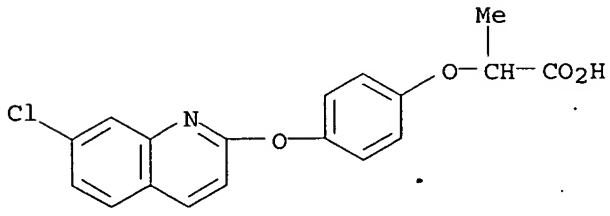


● Na

IT **445041-68-9P**, 2-[4-(7-Fluoroquinolin-2-yloxy)phenoxy]propanoic acid **445041-69-0P 445041-70-3P 445041-75-8P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of quinoline derivs. and there use as antitumor agents)
RN 445041-68-9 CAPLUS
CN Propanoic acid, 2-[4-[(7-fluoro-2-quinolinyl)oxy]phenoxy]- (9CI) (CA INDEX NAME)

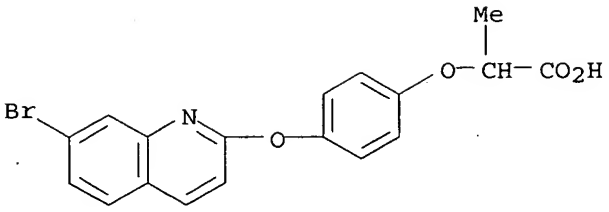


RN 445041-69-0 CAPLUS
CN Propanoic acid, 2-[4-[(7-chloro-2-quinolinyl)oxy]phenoxy]- (9CI) (CA INDEX NAME)



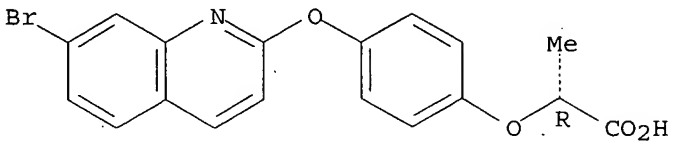
RN 445041-70-3 CAPLUS
CN Propanoic acid, 2-[4-[(7-bromo-2-quinolinyl)oxy]phenoxy]- (9CI) (CA INDEX

NAME)

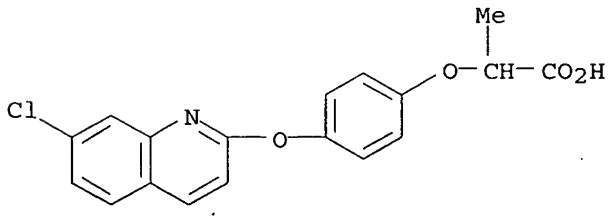


RN 445041-75-8 CAPLUS
CN Propanoic acid, 2-[4-[(7-bromo-2-quinolinyl)oxy]phenoxy]-, (2R)- (9CI) (CA INDEX NAME)

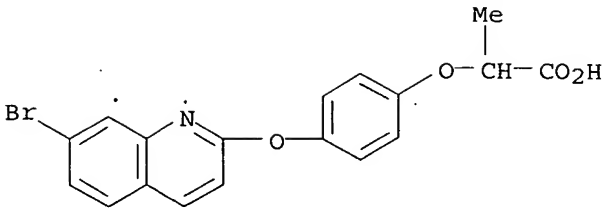
Absolute stereochemistry. Rotation (+).



IT **496802-35-8 496802-40-5 496802-51-8 496836-69-2**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of quinoline derivs. and there use as antitumor agents)
RN 496802-35-8 CAPLUS
CN Propanoic acid, 2-[4-[(7-chloro-2-quinolinyl)oxy]phenoxy]-, sodium salt (9CI) (CA INDEX NAME)



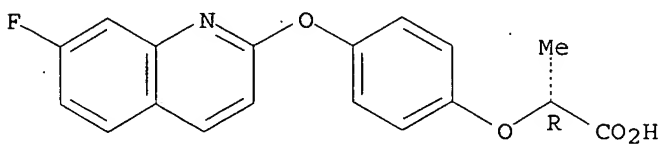
RN 496802-40-5 CAPLUS
CN Propanoic acid, 2-[4-[(7-bromo-2-quinolinyl)oxy]phenoxy]-, sodium salt (9CI) (CA INDEX NAME)



● Na

RN 496802-51-8 CAPLUS
CN Propanoic acid, 2-[4-[(7-fluoro-2-quinolinyl)oxy]phenoxy]-, sodium salt, (2R)- (9CI) (CA INDEX NAME)

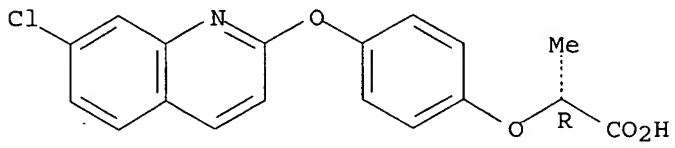
Absolute stereochemistry.



● Na

RN 496836-69-2 CAPLUS
CN Propanoic acid, 2-[4-[(7-chloro-2-quinolinyl)oxy]phenoxy]-, sodium salt, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

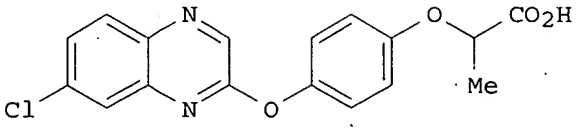


● Na

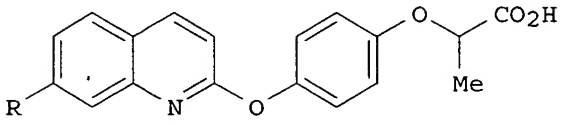
REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:439521 CAPLUS
DOCUMENT NUMBER: 137:140425
TITLE: Synthesis and Biological Evaluation of Some Bioisosteres and Congeners of the Antitumor Agent, 2-{4-[(7-Chloro-2-quinoxalinyl)oxy]phenoxy}propionic Acid (XK469)
AUTHOR(S): Hazeldine, Stuart T.; Polin, Lisa; Kushner, Juiwanna;

White, Kathryn; Bouregeois, Nicole M.; Crantz, Brianna; Palomino, Eduardo; Corbett, Thomas H.; Horwitz, Jerome P.
CORPORATE SOURCE: Barbara Ann Karmanos Cancer Institute, and Walker Cancer Research Institute, Department of Internal Medicine, Division of Hematology and Oncology, Wayne State University School of Medicine, Detroit, MI, USA
SOURCE: Journal of Medicinal Chemistry (2002), 45(14), 3130-3137
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 137:140425
GI



I

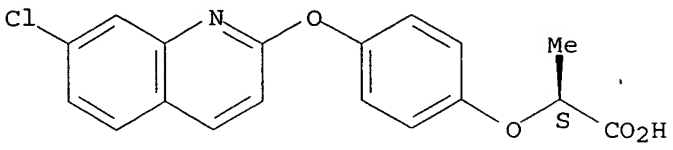


II

AB XK469 (I) was previously identified as a highly and broadly active antitumor agent. Subsequent developmental studies have led to the entry of (R)-(+) I (NSC 698215) into phase 1 clin. trials (NIH UO1-CA62487). The antitumor mechanism of action of I remains to be elucidated, which has prompted a sustained effort to elaborate a pharmacophoric pattern of I. This study focused on a strategy of synthesis and biol. evaluation of topol. based, bioisosteric replacements of the quinoxaline moiety in the lead compound (I) by quinazoline, 1,2,4-benzotriazine, and quinoline ring systems. The synthetic approach to each of the bioisosteres of I utilized methodol. developed in previous work, which is extended to the procurement of the benzoxazole, benzothiazole, pyridine, and pyrazine congeners of I. Only quinoline analogs II, bearing a 7-halo (R = F, Cl, Br, I) or a 7-methoxy substituent (R = MeO), showed antitumor activities (Br > Cl > CH3O > F ≈ I), at levels comparable to or greater than the range of activities manifested by I and corresponding analogs. At high individual dosages, the (S)-(-) enantiomers of I and II (R = Cl, Br) all produce a reversible slowing of nerve-conduction velocity in the mice, the onset of which is characterized by a distinctive dysfunction of the hind legs, causing uncoordinated movements. The condition resolves within 5-10 min. However, at higher dosages, which approach a lethal level, the behavior extended to the front legs, lasting from 20 min to 1 h. By contrast, the (R)-(+) forms of these same agents did not induce the phenomenon of slowing of nerve-conduction velocity.
IT **445041-80-5 445041-81-6**
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); BIOL (Biological study)
(antitumor activity of a quinolinyl aryl ether)
RN 445041-80-5 CAPLUS

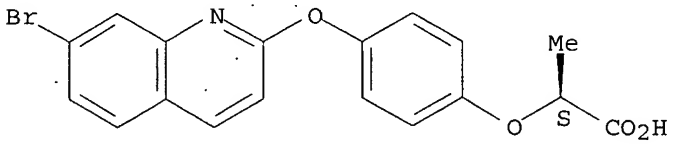
CN Propanoic acid, 2-[4-[(7-chloro-2-quinolinyl)oxy]phenoxy]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

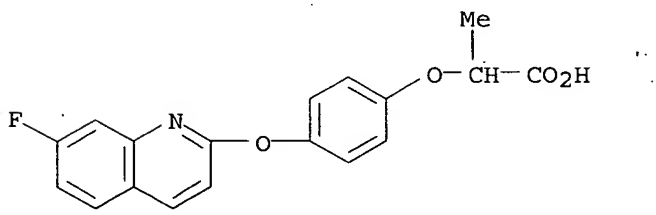


RN 445041-81-6 CAPLUS
CN Propanoic acid, 2-[4-[(7-bromo-2-quinolinyl)oxy]phenoxy]-, (2S)- (9CI) (CA INDEX NAME)

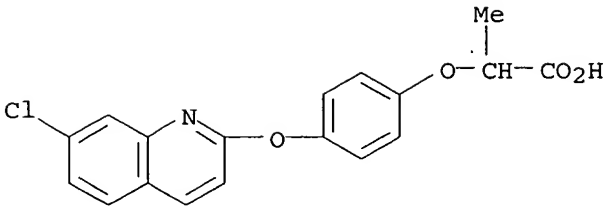
Absolute stereochemistry.



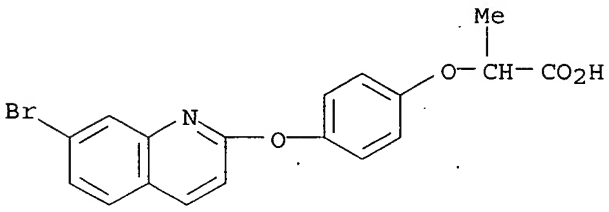
IT **445041-68-9P 445041-69-0P 445041-70-3P 445041-71-4P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation and antitumor activity of quinolinyl aryl ethers via cyclization of N-phenylacrylamides followed by chlorination and aromatic substitution with p-hydroxyphenoxypropanoic acid)
RN 445041-68-9 CAPLUS
CN Propanoic acid, 2-[4-[(7-fluoro-2-quinolinyl)oxy]phenoxy]- (9CI) (CA INDEX NAME)



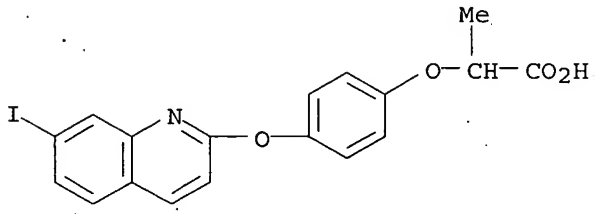
RN 445041-69-0 CAPLUS
CN Propanoic acid, 2-[4-[(7-chloro-2-quinolinyl)oxy]phenoxy]- (9CI) (CA INDEX NAME)



RN 445041-70-3 CAPLUS
CN Propanoic acid, 2-[4-[(7-bromo-2-quinolinyl)oxy]phenoxy]- (9CI) (CA INDEX NAME)

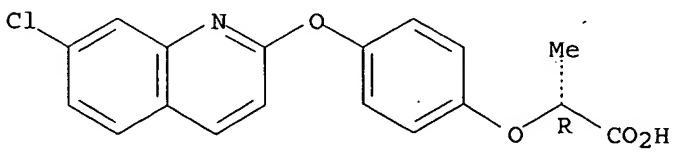


RN 445041-71-4 CAPLUS
CN Propanoic acid, 2-[4-[(7-iodo-2-quinolinyl)oxy]phenoxy]- (9CI) (CA INDEX NAME)



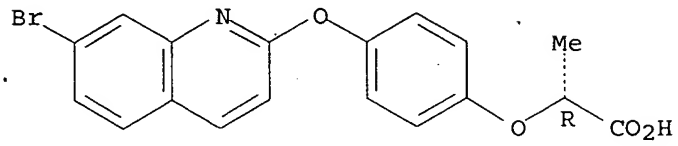
IT **445041-74-7P 445041-75-8P**
RL: PAC (Pharmacological activity); PUR (Purification or recovery); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(stereoselective preparation and antitumor activity of quinolinyl aryl ethers via cyclization of N-phenylacrylamides followed by chlorination and aromatic substitution with optically active p-hydroxyphenoxypropanoic acid)
RN 445041-74-7 CAPLUS
CN Propanoic acid, 2-[4-[(7-chloro-2-quinolinyl)oxy]phenoxy]-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 445041-75-8 CAPLUS
CN Propanoic acid, 2-[4-[(7-bromo-2-quinolinyl)oxy]phenoxy]-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

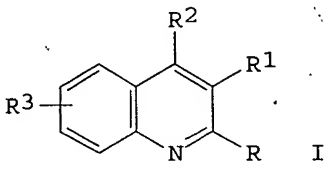


REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

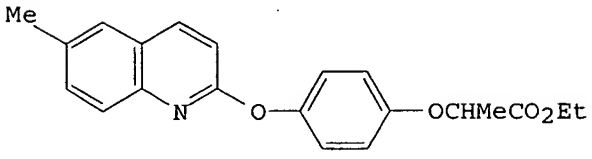
L19 ANSWER 7 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1982:598123 CAPLUS
DOCUMENT NUMBER: 97:198123
TITLE: Quinolineoxyphenoxypropionic acid derivatives and their use as herbicides
INVENTOR(S): Mildenberger, Hilmar; Knorr, Harald; Bauer, Klaus
PATENT ASSIGNEE(S): Hoechst A.-G. , Fed. Rep. Ger.
SOURCE: Ger. Offen., 20 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 3101544	A1	19820819	DE 1981-3101544	19810120
PRIORITY APPLN. INFO.:			DE 1981-3101544	19810120

OTHER SOURCE(S): CASREACT 97:198123
GI



I



II

AB I [one of R or R2, especially R = 4-R4CHMeOC6H4O(R4 = CO2H or a derivative, e.g.
amide) and the other = H, C1-4 alkyl, Ph, Cl, Br; R1 = H, C1-4 alkyl, Cl, Br, cyano, C1-4 carbalkoxy; R3 = H, C1-4 alkyl alkoxy, or dialkylamino, NO2, CF3, halo; n = 0-2] were prepared as herbicides. Thus, 21 g

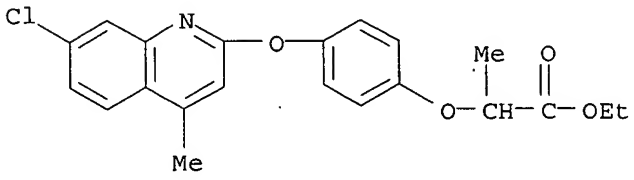
4-HOC6H4OCHMeCO2Et were added dropwise to 2.9 g NaH in 100 mL DMF, 17.7 g 2-chloro-6-methylquinoline added, and the mixture was stirred 2 h at 100° to give 89.2% II.

IT **83596-62-7P**

RL: AGR (Agricultural use); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of, as herbicide)

RN 83596-62-7 CAPLUS

CN Propanoic acid, 2-[4-[(7-chloro-4-methyl-2-quinolinyl)oxy]phenoxy]-, ethyl ester (9CI) (CA INDEX NAME)



```
=> d que l17
L6          163 SEA FILE=CAPLUS ABB=ON  PLU=ON  ("HORWITZ J"/AU OR "HORWITZ J
                P"/AU OR "HORWITZ JEROME"/AU OR "HORWITZ JEROME P"/AU)
L7          155 SEA FILE=CAPLUS ABB=ON  PLU=ON  ("CORBETT T"/AU OR "CORBETT T
                H"/AU OR "CORBETT THOMAS"/AU OR "CORBETT THOMAS H"/AU OR
                "CORBETT THOMAS HUGHES"/AU)
L8           31 SEA FILE=CAPLUS ABB=ON  PLU=ON  ("PALOMINO E"/AU OR "PALOMINO
                EDUARDO"/AU)
L9           45 SEA FILE=CAPLUS ABB=ON  PLU=ON  ("POLIN L"/AU OR "POLIN
                LISA"/AU OR "POLIN LISA A"/AU OR "POLIN LISA ANNE"/AU OR
                "POLIN LISA MARIE"/AU)
L10          12 SEA FILE=CAPLUS ABB=ON  PLU=ON  ("HAZELDINE S"/AU OR "HAZELDINE
                 STEWART T"/AU OR "HAZELDINE STUART"/AU OR "HAZELDINE STUART
                T"/AU OR "HAZELDINE STUART THOMAS"/AU)
L11          46 SEA FILE=CAPLUS ABB=ON  PLU=ON  (L6 AND (L7 OR L8 OR L9 OR
                L10)) OR (L7 AND (L8 OR L9 OR L10)) OR (L8 AND (L9 OR L10)) OR
                (L9 AND L10)
L12          33 SEA FILE=CAPLUS ABB=ON  PLU=ON  L11 NOT (PY>2002 OR AY>2002 OR
                PRY>2002)
L13         329 SEA FILE=CAPLUS ABB=ON  PLU=ON  (L6 OR L7 OR L8 OR L9 OR L10)
L15          44 SEA FILE=CAPLUS ABB=ON  PLU=ON  L13 AND ?AMID?/BI
L16          10 SEA FILE=CAPLUS ABB=ON  PLU=ON  L11 AND L15
L17          36 SEA FILE=CAPLUS ABB=ON  PLU=ON  (L12 OR L16)
```

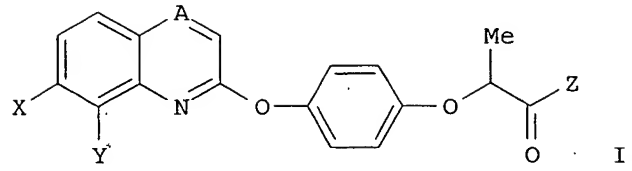
=> d ibib abs hitind l17 tot

L17 ANSWER 1 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:41446 CAPLUS
DOCUMENT NUMBER: 140:111288
TITLE: Preparation of 2-[4-[(7-halo-2-quinolinyl)oxy]phenoxy]propionic acid derivatives and quinoxalinyl analogs as antineoplastic agents
INVENTOR(S): **Horwitz, Jerome P.; Corbett, Thomas H.; Palomino, Eduardo; Polin, Lisa; Hazeldine, Stuart T.**
PATENT ASSIGNEE(S): Wayne State University, USA
SOURCE: PCT Int. Appl., 67 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

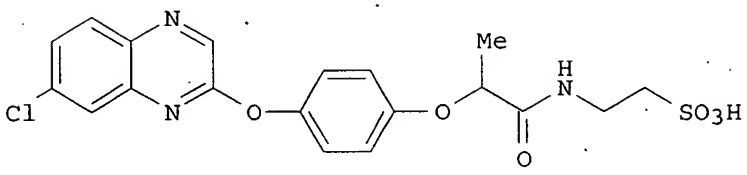
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004005260	A1	20040115	WO 2003-US21062	20030703
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2491612	AA	20040115	CA 2003-2491612	20030703
AU 2003249704	A1	20040123	AU 2003-249704	20030703
US 2004132618	A1	20040708	US 2003-613914	20030703
BR 2003011491	A	20050426	BR 2003-11491	20030703
EP 1539699	A1	20050615	EP 2003-763213	20030703
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
JP 2005532397	T2	20051027	JP 2004-519888	20030703
NO 2005000573	A	20050202	NO 2005-573	20050202

PRIORITY APPLN. INFO.: US 2002-393858P P 20020703
WO 2003-US21062 W 20030703

OTHER SOURCE(S): MARPAT 140:111288
GI



I



II

AB Title compds. I [wherein A = CH or N; X = F, Cl, or Br; Y = H, OH, or alkoxy; Z = an amino acid or heterocycle; and pharmaceutically acceptable salts thereof] were prepared and tested in vivo as antitumor agents. Preferred compds. of the invention and their pharmaceutical compns. are more potent and less toxic than the known antitumor agent, 2-[4-[(7-chloro-2-quinoxalinyl)oxy]phenoxy]propanoic acid sodium salt (XK 469), and have a different metabolic profile than XK 469. For example, XK 469 was refluxed with SOCl2 for 1 h and the resulting acid chloride treated with β-aminoethylsulfonate (taurine) and 1M NaOH in THF to give II•Na (74%). Chiral HPLC separation afforded the enantiomers. (R)-II•Na was well tolerated in mice at a total dose of 1610 mg/kg i.v. and was highly active (T/C = 0%, log cell kill = 4.2) against early stage murine mammary adenocarcinoma 16/C. No adverse symptoms or cures were noted post injection.

IC ICM C07D215-22
ICS C07D241-44; A61K031-47; A61K031-498; A61P035-00

CC 27-17 (Heterocyclic Compounds (One Hetero Atom))
Section cross-reference(s): 1, 63

IT 347162-71-4P 347162-73-6P 445041-75-8P, (R)-2-[4-[(7-Bromo-2-quinolinyl)oxy]phenoxy]propionic acid 643752-97-0P 643753-00-8P, 2-[4-[(7-Chloro-2-quinolinyl)oxy]phenoxy]-N,N-**dimethylpropionamide** 643753-13-3P 646505-48-8P 646505-49-9P, (R)-[[2-[4-[(7-Bromoquinolin-2-yl)oxy]phenoxy]propionyl]amino]acetic acid 646505-50-2P, (R)-[[2-[4-[(7-Chloroquinoxalin-2-yl)oxy]phenoxy]propionyl]amino]acetic acid 646505-51-3P
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(antitumor agent; preparation of [[(haloquinolinyl)oxy]phenoxy]propionic acid derivs. and quinoxalinyl analogs as antineoplastic agents)

IT 445041-74-7P, (R)-2-[4-[(7-Chloro-2-quinolinyl)oxy]phenoxy]propionic acid 643752-98-1P, 2-[4-[(7-Bromo-2-quinolinyl)oxy]phenoxy]-N-**methylpropionamide** 643753-02-0P 643753-03-1P 643753-05-3P, [[2-[4-[(7-Bromoquinolin-2-yl)oxy]phenoxy]propionyl]amino]acetic acid 643753-06-4P, [[2-[4-[(7-Chloroquinoxalin-2-yl)oxy]phenoxy]propionyl]amino]acetic acid 647026-61-7P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(antitumor agent; preparation of [[(haloquinolinyl)oxy]phenoxy]propionic acid derivs. and quinoxalinyl analogs as antineoplastic agents)

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 2 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:41220 CAPLUS
DOCUMENT NUMBER: 140:99632
TITLE: Preparation of therapeutic **amides** as antitumor agents
INVENTOR(S): **Horwitz, Jerome P.; Corbett, Thomas H.; Palomino, Eduardo; Polin, Lisa; Hazeldine, Stuart T.**
PATENT ASSIGNEE(S): Wayne State University, USA
SOURCE: PCT Int. Appl., 52 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004004651	A2	20040115	WO 2003-US21126	20030703
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004132618	A1	20040708	US 2003-613914	20030703
PRIORITY APPLN. INFO.:			US 2002-393858P P	20020703

OTHER SOURCE(S): MARPAT 140:99632

AB **Amides**, e.g., 2-{4-((7-bromo-2-quinolinyl)oxy)phenoxy} **propionmethylamide**, {2-{4-(7-bromoquinolin-2-yloxy)phenoxy}propionylamino}acetic acid, or 4-(7-chloro-2-quinolinyl)oxyphenoxypropionylaminoethanesulfonic acid,are prepared for use as effective antitumor agents. The invention also provides pharmaceutical compns. comprising the above compound, intermediates useful for preparing the compds., and methods for administering the compds. to a mammal. Thus, sodium (2-(4-(7-chloro-2-quinolinyl)oxy)phenoxy)propionylaminoethanesulfonate was prepared in a series of steps by starting from Et vinyl ether with oxalyl chloride followed by treatment with substituted anilines cyclization, and subsequent treatment with 2-(4-hydroxyphenoxy)propionic acid. Tablets contained the above compound 100.0, lactose 77.5, Povidone 15.0, Croscarmellose sodium 12.0, microcryst. cellulose 92.5, and Mg stearate 3.0 mg/tablet. The compound had activity against adenocarcinoma.

IC ICM A61K
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1, 28
ST therapeutic **amide** antitumor prepn
IT Carcinoma
(adenocarcinoma; preparation of therapeutic **amides** as antitumor agents)
IT Drug delivery systems
(aerosols; preparation of therapeutic **amides** as antitumor agents)
IT Drug delivery systems

(capsules; preparation of therapeutic **amides** as antitumor agents)
IT Drug delivery systems
(injections; preparation of therapeutic **amides** as antitumor agents)
IT Antitumor agents
Neoplasm
(preparation of therapeutic **amides** as antitumor agents)
IT **Amides**, biological studies
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of therapeutic **amides** as antitumor agents)
IT Drug delivery systems
(tablets; preparation of therapeutic **amides** as antitumor agents)
IT 23952-31-0P 59412-12-3P 99455-13-7P 160893-07-2P 455955-27-8P
RL: BYP (Byproduct); PREP (Preparation)
(preparation of therapeutic **amides** as antitumor agents)
IT 347162-71-4P 347162-73-6P 643752-97-0P 643752-98-1P 643753-00-8P
643753-02-0P 643753-03-1P 643753-05-3P 643753-06-4P 643753-11-1P
643753-12-2P 643753-13-3P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of therapeutic **amides** as antitumor agents)
IT 56-40-6, Glycine, reactions 79-37-8, Oxalyl chloride 107-35-7, Taurine
108-42-9 108-44-1, reactions 109-92-2, Ethyl vinyl ether 372-19-0
536-90-3 591-19-5 67648-61-7 94050-90-5 99471-66-6,
trans-3-Ethoxyacryloyl chloride
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of therapeutic **amides** as antitumor agents)
IT 613-77-4P 4053-33-2P 4053-35-4P 4295-12-9P 22614-72-8P
23981-22-8P 23981-26-2P 49609-15-6P 99455-15-9P 99465-09-5P
99465-10-8P 99465-18-6P 148136-14-5P 157435-10-4P 157542-91-1P
157542-92-2P 160893-04-9P 445041-59-8P 445041-60-1P 445041-63-4P
445041-64-5P 445041-65-6P 445041-68-9P 445041-69-0P 445041-70-3P
445041-72-5P 445041-73-6P 445041-74-7P 445041-75-8P 643752-95-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of therapeutic **amides** as antitumor agents)

L17 ANSWER 3 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:245057 CAPLUS
DOCUMENT NUMBER: 139:390795
TITLE: Discovery and Preclinical Antitumor Efficacy Evaluations of LY32262 and LY33169
AUTHOR(S): **Corbett, Thomas H.**; White, Kathryn; **Polin, Lisa**; Kushner, Juiwanna; Paluch, Jennifer; Shih, Chuan; Grossman, Cora Sue
CORPORATE SOURCE: Barbara Ann Karmanos Cancer Institute, Wayne State University School of Medicine, Detroit, MI, 48201, USA
SOURCE: Investigational New Drugs (2003), 21(1), 33-45
CODEN: INNDDK; ISSN: 0167-6997
PUBLISHER: Kluwer Academic Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The discoveries of a new antitumor agent (LY32262) (N-[2,4-dichlorobenzoyl]**phenylsulfonamide**) and a close analog (LY33169) are described. For this discovery, a disk-diffusion-soft-agar-colony-formation-assay was used to screen a portion of the Eli Lilly inventory,

with the evaluation of each agent against normal cells, leukemic cells and several solid tumors, including a multidrug-resistant solid tumor (with marked selective cytotoxicity for Colon-38 and Human-Colon-15/MDR compared to normal fibroblasts and L1210 leukemic cells characterizing the discovery). In mice, LY32262 and/or LY33169 had curative activity against Colon Adenocarcinoma-38, Human Colon-116, Human Prostate LNCaP, and Human Breast WSU-Br-1. In addition, many other tumors were highly sensitive: Panc-03=2.4 log kill (LK); Panc-02=2.9-4.1 LK; Squamous Lung LC-12=2.1 LK; Colon-26=2.2 LK; AML1498=2.7 LK; Human Sm Cell Lung DMS-273=6.3 LK; Human Squamous Lung 165=3.7 LK; Human Ovarian BG-1=3.7 LK; Human Colon CX-1 (H29)=1.6 LK; Human Colon-15/MDR (a p-glycoprotein pos. multidrug resistant tumor)=2.3 LK; Human CNS-gliosarcoma-SF295=3.8 LK. Several tumors were only marginally responsive or totally unresponsive: Mammary Adenocarcinoma-16/C=0.6 LK; Mammary Adenocarcinoma-17=no kill; Colon Adenocarcinoma-11=no kill; L1210 leukemia=1.3 LK; Human Prostate PC-3=0.5 LK; Human Adenosquamous Lung H125=no kill; and Human Breast Adenocarcinoma MX-1=0.9 LK. There was no absolute tissue of origin correlation with antitumor efficacy, although colon tumors were most responsive and mammary tumors least responsive. The cause of the "hit and miss" efficacy has not been determined

CC 1-6 (Pharmacology)

REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 4 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2002:439521 CAPLUS

DOCUMENT NUMBER: 137:140425

TITLE: Synthesis and Biological Evaluation of Some Bioisosteres and Congeners of the Antitumor Agent, 2-{4-[(7-Chloro-2-quinoxalinyl)oxy]phenoxy}propionic Acid (XK469)

AUTHOR(S): **Hazeldine, Stuart T.**; **Polin, Lisa**; Kushner, Juiwanna; White, Kathryn; Bouregeois, Nicole M.; Crantz, Brianna; **Palomino, Eduardo**; **Corbett, Thomas H.**; **Horwitz, Jerome P.**

CORPORATE SOURCE: Barbara Ann Karmanos Cancer Institute, and Walker Cancer Research Institute, Department of Internal Medicine, Division of Hematology and Oncology, Wayne State University School of Medicine, Detroit, MI, USA

SOURCE: Journal of Medicinal Chemistry (2002), 45(14), 3130-3137
CODEN: JMCMAR; ISSN: 0022-2623

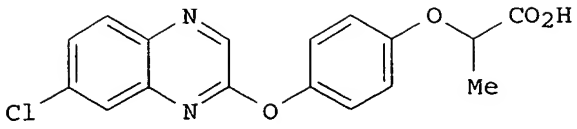
PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

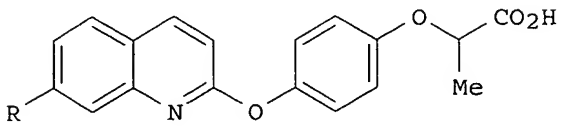
LANGUAGE: English

OTHER SOURCE(S): CASREACT 137:140425

GI



I



II

AB XK469 (I) was previously identified as a highly and broadly active antitumor agent. Subsequent developmental studies have led to the entry of (R)-(+) I (NSC 698215) into phase 1 clin. trials (NIH UO1-CA62487). The antitumor mechanism of action of I remains to be elucidated, which has prompted a sustained effort to elaborate a pharmacophoric pattern of I. This study focused on a strategy of synthesis and biol. evaluation of topol. based, bioisosteric replacements of the quinoxaline moiety in the lead compound (I) by quinazoline, 1,2,4-benzotriazine, and quinoline ring systems. The synthetic approach to each of the bioisosteres of I utilized methodol. developed in previous work, which is extended to the procurement of the benzoxazole, benzothiazole, pyridine, and pyrazine congeners of I. Only quinoline analogs II, bearing a 7-halo (R = F, Cl, Br, I) or a 7-methoxy substituent (R = MeO), showed antitumor activities (Br > Cl > CH3O > F ≈ I), at levels comparable to or greater than the range of activities manifested by I and corresponding analogs. At high individual dosages, the (S)-(-) enantiomers of I and II (R = Cl, Br) all produce a reversible slowing of nerve-conduction velocity in the mice, the onset of which is characterized by a distinctive dysfunction of the hind legs, causing uncoordinated movements. The condition resolves within 5-10 min. However, at higher dosages, which approach a lethal level, the behavior extended to the front legs, lasting from 20 min to 1 h. By contrast, the (R)-(+) forms of these same agents did not induce the phenomenon of slowing of nerve-conduction velocity.

CC 27-17 (Heterocyclic Compounds (One Hetero Atom))
Section cross-reference(s): 1

IT Asymmetric synthesis and induction
(stereoselective preparation and antitumor activity of quinolinyl aryl ethers via cyclization of N-**phenylacrylamides** followed by chlorination and aromatic substitution with optically active p-hydroxyphenoxypropanoic acid)

IT 76578-20-6P 445041-68-9P 445041-69-0P 445041-70-3P 445041-71-4P 445041-72-5P 445041-73-6P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation and antitumor activity of quinolinyl aryl ethers via cyclization of N-**phenylacrylamides** followed by chlorination and aromatic substitution with p-hydroxyphenoxypropanoic acid)

IT 99465-18-6 445041-59-8 445041-60-1 445041-61-2 445041-62-3 445041-63-4 445041-64-5
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation and antitumor activity of quinolinyl aryl ethers via cyclization of N-**phenylacrylamides** followed by chlorination and aromatic substitution with p-hydroxyphenoxypropanoic acid)

IT 613-77-4P, Quinoline, 2,7-dichloro- 1810-72-6P, Quinoline, 2,6-dichloro- 4295-12-9P, Quinoline, 2-chloro-7-methyl- 49609-15-6P, Quinoline,

2-chloro-7-methoxy- 99455-15-9P, Quinoline, 7-bromo-2-chloro-
445041-65-6P 445041-66-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and antitumor activity of quinolinyl aryl ethers via cyclization of N-**phenylacrylamides** followed by chlorination and aromatic substitution with p-hydroxyphenoxypropanoic acid)

IT 445041-74-7P 445041-75-8P
RL: PAC (Pharmacological activity); PUR (Purification or recovery); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(stereoselective preparation and antitumor activity of quinolinyl aryl ethers via cyclization of N-**phenylacrylamides** followed by chlorination and aromatic substitution with optically active p-hydroxyphenoxypropanoic acid)

REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 5 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:328664 CAPLUS
DOCUMENT NUMBER: 137:345674
TITLE: Lack of in vitro - in vivo correlation of a novel investigational anticancer agent, SH 30
AUTHOR(S): Poondru, Srinivasu; Parchment, Ralph E.; Purohit, Vivek; LoRusso, Patricia; **Horwitz, Jerome P.**; **Hazeldine, Stuart T.**; **Polin, Lisa**; **Corbett, Thomas**; Jasti, Bhaskara R.
CORPORATE SOURCE: Division of Haematology & Oncology, Department of Internal Medicine, Wayne State University, MI, USA
SOURCE: Investigational New Drugs (2002), 20(1), 23-33
CODEN: INNDDK; ISSN: 0167-6997
PUBLISHER: Kluwer Academic Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In solid tumors, the reasons for the lack of in vitro and in vivo correlation of drug activities are multifold and includes permeability to the tumor cells, interstitial hypertension and metabolic degradation So, it is important to study the permeability and metabolic disposition of new compds. early in discovery and development of anticancer drugs. An exptl. anti-cancer drug, SH 30 demonstrated highly selective and potent cytotoxic activity against a number of multi-drug resistant tumor cell lines in vitro. However, it was inactive in a murine tumor model. This study was conducted to identify the barriers that result in lack of correlation between in vitro and in vivo cytotoxic activity of novel anticancer agents. Two important barriers: phys. (permeability) and metabolic (enzymic inactivation) to poor delivery of SH 30 to solid tumors were investigated in this study. Tumors were sliced to sep. the vascular and avascular sections. The concns. of the drug at various regions of the tumor after single and multiple doses were investigated to determine the permeability barrier. The permeability barrier was also probed using two in vitro model systems, namely, matrigel films representing extracellular matrix and caco-2 multilayer cell cultures that simulate solid tumors. The drug and its metabolite concns. were determined in the plasma and tumors to determine the metabolic barrier to the drug cytotoxic action. The metabolic barrier was further probed using in vitro mouse hepatocytes and liver microsome prepns. Our examination revealed the metabolic barrier to be the major contributor to the ineffectiveness of SH 30 in vivo. Examination of concentration of the drug across various regions of the tumor corroborated by data from in vitro permeation studies suggested that, for SH 30, permeability barrier did not exist. After single injection, the concns.

of SH 30 and its metabolites in plasma and tumor were comparable to another investigational drug with similar features (XK 469). Contrary to day 1, after 8 consecutive days of administration, SH 30 concns. were significantly lower, while the metabolites concns. were higher, suggesting extensive metabolism due to induction of enzyme(s). The in vitro hepatocytes and liver microsome results also showed SH 30 biotransformation to the same metabolites. Neither drug penetration, nor drug distribution into regions of the tumors distal to vasculature were impeded. The inactivity of SH 30 in vivo is primarily due to induction of extensive metabolism to inactive metabolites. This metabolism prevents adequate drug levels being achieved in the tumor.

CC 1-6 (Pharmacology)
Section cross-reference(s): 14, 63

REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 6 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:328662 CAPLUS
DOCUMENT NUMBER: 137:345673
TITLE: Preclinical efficacy evaluations of XK-469: Dose schedule, route and cross-resistance behavior in tumor bearing mice
AUTHOR(S): **Polin, Lisa**; White, Kathryn; Kushner, Juiwanna; Paluch, Jennifer; Simpson, Chiab; Pugh, Susan; Edelstein, Matthew K.; **Hazeldine, Stuart**; Fontana, Joseph; LoRusso, Patricia; **Horwitz, Jerome P.**; **Corbett, Thomas H.**
CORPORATE SOURCE: Barbara Ann Karmanos Cancer Institute, Wayne State University, Detroit, MI, USA
SOURCE: Investigational New Drugs (2002), 20(1), 13-22
CODEN: INNDDK; ISSN: 0167-6997
PUBLISHER: Kluwer Academic Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English

AB XK-469 is advancing to Phase I clin. trials. Preclin. studies were carried out to assist in clin. applications. Single dose IV treatment with XK-469 produced lethality (LD20 to LD 100) above 142 mg/kg. Optimum treatment required total dosages of 350 to 600 mg/kg. Furthermore, high individual IV dosages (100 to 142 mg/kg) were poorly tolerated, producing substantial weight loss (8 to 18% of body weight), poor appearance, and slow recovery (8 to 12 days). A 1-h infusion of dosages more than 140 mg/kg, or BID injections 6 h apart, did not reduce lethality. However, lower individual dosages of 40 to 50 mg/kg/injection IV were well tolerated and could be given daily to reach an optimum total dose with minimal toxicities. Likewise, 75 mg/kg/injection IV could be used every other day to reach optimal treatment. The necropsy profiles of deaths from toxic dosages were essentially identical regardless of schedule (deaths 4 to 7 days post treatment). Paralytic ileus or gastroparesis; GI epithelial damage; and marrow toxicity. Interestingly, the key lethal events were rapidly reversible and simple to overcome with lower dosages given daily or every other day. Based on these results, the high dose, Q21day schedule should be avoided in clin. applications. Instead, a split dose regimen is recommended (e.g., daily, every other day, or twice weekly). XK-469 was also well tolerated by the oral route, requiring 35% higher dosages PO to reach the same efficacy and toxicity as produced IV. XK-469 resistance was produced by optimum treatments of IV implanted L1210 leukemia over seven passage generations. This leukemia subline (L1210/XK469) had reduced sensitivity to VP-16 (with a 4.0 log kill in IV implanted L1210/XK469 compared to an 8.0 log kill against IV implanted

L1210/0). It also had a reduction in the sensitivity to 5-FU (with a 2.0 log kill in the implanted L1210/XK469 compared to a 4.0 log kill against IV implanted L1210/0). Other agents were approx. as active against the resistant tumor, including: Ara-C, Gemzar, Cytoxan, BCNU, DTIC, and CisDDPT. No case of collateral sensitivity was observed; i.e., no agent was markedly more active against the resistant subline L1210/XK-469 than against the parent tumor in mice.

CC 1-6 (Pharmacology)

REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 7 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2001:301100 CAPLUS

DOCUMENT NUMBER: 135:76849

TITLE: Design, Synthesis, and Biological Evaluation of Analogues of the Antitumor Agent, 2-{4-[(7-Chloro-2-quinoxalinyl)oxy]phenoxy}propionic Acid (XK469)

AUTHOR(S): **Hazeldine, Stuart T.**; **Polin, Lisa**; Kushner, Juiwanna; Paluch, Jennifer; White, Kathryn; Edelstein, Matthew; **Palomino, Eduardo**; **Corbett, Thomas H.**; **Horwitz, Jerome P.**

CORPORATE SOURCE: Department of Internal Medicine Division of Hematology and Oncology, Wayne State University School of Medicine, Detroit, MI, 48201, USA

SOURCE: Journal of Medicinal Chemistry (2001), 44(11), 1758-1776
CODEN: JMCMAR; ISSN: 0022-2623

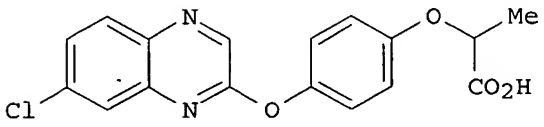
PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

OTHER SOURCE(S): CASREACT 135:76849

GI



I

AB 2-{4-[(7-Chloro-2-quinoxalinyl)oxy]phenoxy}propionic acid (XK469) I is among the most highly and broadly active antitumor agents to have been evaluated and scheduled to enter clin. trials in 2001. The mechanism or mechanisms of action of I remain to be elaborated. Accordingly, an effort was initiated to establish a pharmacophore hypothesis to delineate the requirements of the active site, via a comprehensive program of synthesis of analogs of I and evaluation of the effects of structural modification(s) on solid tumor activity. The strategy formulated chose to dissect the two-dimensional parent structure into three regions: I, ring A of quinoxaline; II, the hydroquinone connector linkage; and III, the lactic acid moiety-to determine the resultant in vitro and in vivo effects of chemical alterations in each region. Neither the A-ring unsubstituted nor the B-ring 3-chloro-regioisomer of I showed antitumor activity. The modulating antitumor effect(s) of substituents of differing electronegativities, located at the several sites comprising the A-ring of region I, were next ascertained. Thus, a halogen substituent, located at the 7-position of a 2-{4-[(2-quinoxalinyl)oxy]phenoxy}propionic acid, generated the most highly and broadly active antitumor agents. A Me,

methoxy, or an azido substituent at this site generated a much less active structure, whereas 5-, 6-, 8-chloro-, 6-, 7-nitro, and 7-amino derivs. all proved to be essentially inactive. When the connector linkage (region II) of I was changed from that of a hydroquinone to either a resorcinol or a catechol derivative, all antitumor activity was lost. Of the carboxylic acid derivs. of I (region III), i.e., CONH2, CONHMe, CONMe2, CONHOH, CONHNH2, CN, or CN4H (tetrazole), only the monomethyl- and N,N-**dimethylamides** proved to be active.

CC 28-18 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 8 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:672229 CAPLUS
DOCUMENT NUMBER: 134:212596
TITLE: In-vitro and iv-vivo activity of SH 30, a novel anticancer compound
AUTHOR(S): Jasti, B. R.; Poondru, S.; Purohit, V.; Parchment, R.; Grieshaber, C.; **Horwitz, J. P.**; **Hazeldine, S.**; **Polin, L.**; **Corbett, T.**
CORPORATE SOURCE: Department of Pharmaceutical Sciences Department of Internal Medicine, Wayne State University, MI, USA
SOURCE: Proceedings of the International Symposium on Controlled Release of Bioactive Materials (2000), 27th, 602-603
CODEN: PCRMEY; ISSN: 1022-0178
PUBLISHER: Controlled Release Society, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB SH 30 exhibited in vitro activity comparable to XK 469 with respect to selectivity and cytotoxicity but failed to show any effect in vivo, due to extensive metabolism to inactive metabolite and tolerance development through enzyme induction.

CC 63-6 (Pharmaceuticals)
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 9 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:717491 CAPLUS
DOCUMENT NUMBER: 132:189368
TITLE: Preclinical efficacy of thioxanthone SR271425 against transplanted solid tumors of mouse and human origin
AUTHOR(S): **Corbett, Thomas H.**; Panchapor, Chiab; **Polin, Lisa**; Lowichik, Nancy; Pugh, Susan; White, Kathryn; Kushner, Juiwanna; Meyer, Jennifer; Czarnecki, Jennifer; Chinnukroh, Salina; Edelstein, Matthew; LoRusso, Patricia; Heilbrun, Lance; **Horwitz, Jerome P.**; Grieshaber, Charles; Perni, Robert; Wentland, Mark; Coughlin, Susan; Elenbaas, Steven; Philion, Richard; Rake, James
CORPORATE SOURCE: Karmanos Cancer Institute, Wayne State University School of Medicine, Detroit, MI, USA
SOURCE: Investigational New Drugs (1999), 17(1), 17-27
CODEN: INNDDK; ISSN: 0167-6997
PUBLISHER: Kluwer Academic Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A highly active and broadly active thioxanthone has been identified: N-[1-[[2-(Diethylamino)ethyl]amino]-7-methoxy-9-oxo-9H-thioxanthen-4-yl] **methylformamide** (SR271425, BCN326862, WIN71425). In preclin. testing against a variety of s.c. growing solid tumors, the following %T/C and Log10 tumor cell kill (LK) values were obtained: Panc-03 T/C = 0, 5/5 cures; Colon-38 (adv. stage) T/C = 0, 3/5 cures, 4.9 LK; Mam-16/C T/C = 0, 3.5 LK; Mam-17/0 T/C = 0, 2.8 LK; Colon-26 T/C = 0, 1/5 cures, 3.2 LK; Colon-51 T/C= 0, 2.7 LK; Panc-02 T/C = 0, 3.1 LK; B16 Melanoma T/C = 13%, 4.0 LK; Squamous Lung-LC12 (adv. stage) T/C = 14%, 4.9 LK; BG-1 human ovarian T/C = 16%, 1.3 LK; WSU-Br1 human breast T/C = 25%, 0.8 LK. The agent was modestly active against doxorubicin (Adr)-resistant solid tumors: Mam-17/Adr T/C =23%, 0.8 LK; and Mam-16/C/Adr T/C = 25%, 1.0 LK, but retained substantial activity against a taxol-resistant tumor: Mam-16/C/taxol T/C = 3%, 2.4 LK. SR271425 was highly active against IV implanted leukemias, L1210 6.3 LK and AML1498 5.3 LK. The agent was equally active both by the IV and oral routes of administration, although requiring approx. 30% higher dose by the oral route. Based on its preclin. antitumor profile, it may be appropriate to evaluate SR271425 in clin. trials.

CC 1-6 (Pharmacology)

REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 10 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1999:492998 CAPLUS

DOCUMENT NUMBER: 131:331811

TITLE: Preclinical antitumor activity of XK469 (NSC 656889)

AUTHOR(S): LoRusso, Patricia M.; Parchment, Ralph; Demchik, Lisa; Knight, Juianna; **Polin, Lisa**; Dzubow, Janet; Behrens, Carl; Harrison, Barbara; Trainor, George; **Corbett, Thomas H.**

CORPORATE SOURCE: Karmanos Cancer Institute, Wayne State University School of Medicine, Detroit, MI, USA

SOURCE: Investigational New Drugs (1999), Volume Date 1998-1999, 16(4), 287-296
CODEN: INNDDK; ISSN: 0167-6997

PUBLISHER: Kluwer Academic Publishers

DOCUMENT TYPE: Journal

LANGUAGE: English

AB XK469 (NSC 656889) is a water-soluble member of the novel quinoxaline family of antitumor agents. In vitro, XK469 demonstrated selective cytotoxicity for several murine solid tumors including colorectal and mammary adenocarcinoma cell lines, when compared to both leukemia and normal epithelial cells. In vivo, XK469 was active against 7/7 murine tumors tested, including pancreatic ductal carcinomas #02 and #03, colon adenocarcinomas #38 and #51/A, mammary adenocarcinoma #16/C and the Adriamycin-resistant mammary adenocarcinomas #16/C/ADR and #17/ADR. XK469 was efficacious both i.v. and orally. Regardless of dosing schedule, conventional mice tolerated higher total doses than SCID or nu/nu mice did. Despite these reduced doses, XK469 was active against xenografts of 4/6 human tumor lines including mammary adenocarcinoma MX-1, the small cell lung cancer DMS 273, the prostate model LNCaP and the CNS tumor SF295. The lower doses in the xenograft studies were below curative levels. The dose-limiting toxicity appeared to be myelosuppression with rapid host recovery (5-8 days), and in vitro assays of XK469 toxicity to murine bone marrow neutrophil progenitors CFU-GM (colony forming unit-granulocyte/macrophage) demonstrated concentration-dependent toxicity from 0.5-30 μg/mL. The difference in drug tolerance between BDF1 and SCID mice was detected in vitro as a 3-fold difference in the IC90 for CFU-GM,

despite similar IC50 values. Comparative in vitro hematotoxicol. studies revealed that human bone marrow CFU-GM tolerated XK469 as well as their SCID counterparts (IC90 values 5.7 vs. 7.4 μg/mL). Based on comparison with previously tested anti-cancer agents, these data suggest that humans will be able to tolerate XK469 doses that are efficacious against human tumor xenografts.

CC 1-6 (Pharmacology)

REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 11 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1999:138449 CAPLUS

DOCUMENT NUMBER: 131:33

TITLE: In vivo methods for screening and preclinical testing: use of rodent solid tumors for drug discovery

AUTHOR(S): **Corbett, Thomas**; Valeriote, Fred; LoRusso, Patricia; **Polin, Lisa**; Panchapor, Chiab; Pugh, Susan; White, Kathryn; Knight, Juiwanna; Demchik, Lisa; Jones, Julie; Jones, Lynne; Lisow, Loretta

CORPORATE SOURCE: Div. Hematol. Oncol., Wayne Stat Univ. School Med., Detroit, MI, USA

SOURCE: Anticancer Drug Development Guide (1997), 75-99. Editor(s): Teicher, Beverly A. Humana: Totowa, N. J. CODEN: 67LMAC

DOCUMENT TYPE: Conference; General Review

LANGUAGE: English

AB A review with 45 refs. of rodent models and protocol designs that have been used in the discovery of antitumor agents currently in clin. usage.

CC 1-0 (Pharmacology)
Section cross-reference(s): 14

REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 12 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1998:787599 CAPLUS

DOCUMENT NUMBER: 130:204665

TITLE: Preclinical antitumor efficacy of analogs of XK469: sodium-(2-[4-(7-chloro-2-quinoxalinyloxy)phenoxy]propionate)

AUTHOR(S): **Corbett, Thomas H.**; LoRusso, Patricia; Demchick, Lisa; Simpson, Chiab; Pugh, Susan; White, Kathryn; Kushner, Juiwanna; **Polin, Lisa**; Meyer, Jennifer; Czarnecki, Jennifer; Heilbrun, Lance; **Horwitz, Jerome P.**; Gross, Janet L.; Behrens, Carl H.; Harrison, Barbara A.; McRipley, Ron J.; Trainor, George

CORPORATE SOURCE: School of Medicine, Wayne State University, Detroit, USA

SOURCE: Investigational New Drugs (1998), 16(2), 129-139 CODEN: INNDDK; ISSN: 0167-6997

PUBLISHER: Kluwer Academic Publishers

DOCUMENT TYPE: Journal

LANGUAGE: English

AB A series of quinoxaline analogs of the herbicide Assure was found to have selective cytotoxicity for solid tumors of mice in a disk-diffusion-soft-agar-colony-formation-assay compared to L1210 leukemia. Four agents without selective cytotoxicity and 14 agents with selective cytotoxicity were evaluated in vivo for activity against a solid tumor. The four

agents without selective cytotoxicity in the disk-assay were inactive in vivo (T/C > 42%). Thirteen of the fourteen agents with selectivity in the disk-assay were active in vivo (T/C < 42%). Five of the agents had curative activity. These five agents had a halogen (F, Cl, Br) in the 7-position (whereas Assure had a Cl in the 6 position). All agents with curative activity were either a carboxylic acid, or a derivative thereof, whereas Assure is the Et ester of the carboxylic acid. All other structural features were identical between Assure and the curative agents. Assure had no selective cytotoxicity for solid tumors in the disk-assay, and was devoid of antitumor activity. The analog XK469 is in clin. development.

CC 1-3 (Pharmacology)
REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 13 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:778625 CAPLUS
DOCUMENT NUMBER: 128:70312
TITLE: Discovery of cryptophycin-1 and BCN-183577: examples of strategies and problems in the detection of antitumor activity in mice
AUTHOR(S): **Corbett, Thomas H.**; Valeriote, Frederick A.; Demchik, Lisa; Lowichik, Nancy; **Polin, Lisa**; Panchapor, Chiab; Pugh, Susan; White, Kathryn; Kushner, Juiwanna; Rake, James; Wentland, Mark; Golakoti, Trimurtulu; Hetzel, Carl; Ogino, Junichi; Patterson, Gregory; Moore, Richard
CORPORATE SOURCE: Division of Hematology and Oncology, Department of Internal Medicine, Wayne State University School of Medicine, Detroit, USA
SOURCE: Investigational New Drugs (1997), 15(3), 207-218
CODEN: INNDDK; ISSN: 0167-6997
PUBLISHER: Kluwer Academic Publishers
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 15 refs. Historically, many new anticancer agents were first detected in a prescreen, usually consisting of a mol./biochem. target or a cellular cytotoxicity assay. The agent then progressed to in vivo evaluation against transplanted human or mouse tumors. If the investigator had a large drug supply and ample resources, multiple tests were possible, with variations in tumor models, tumor and drug routes, dose-decrements, dose-schedules, number of groups, etc. However, in most large programs involving several hundred in vivo tests yearly, resource limitations and drug supply limitations have usually dictated a single trial. Under such restrictive conditions, we have implemented a flexible in vivo testing protocol. With this strategy, the tumor model is dictated by in vitro cellular sensitivity; drug route by water solubility (with water soluble agents injected i.v.); dosage decrement by drug supply, dose-schedule by toxicities encountered, etc. In this flexible design, many treatment parameters can be changed during the course of treatment (e.g., dose and schedule). The discovery of two active agents is presented (Cryptophycin-1 and Thioxanthone BCN 183577). Their activity would have been missed if they were tested i.p., the usual drug route used in discovery protocols. It is also likely that they would have been missed with an easy to execute fixed protocol design, even if injected IV.
CC 1-0 (Pharmacology)
REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 14 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:638466 CAPLUS
DOCUMENT NUMBER: 127:288310
TITLE: Induction of the Estrogen Specific Mitogenic Response of MCF-7 Cells by Selected Analogs of Estradiol-17β: A 3D QSAR Study
AUTHOR(S): Wiese, Thomas E.; **Polin, Lisa A.**; **Palomino, Eduardo**; Brooks, S. C.
CORPORATE SOURCE: Department of Biochemistry, Wayne State University School of Medicine, Detroit, MI, 48201, USA
SOURCE: Journal of Medicinal Chemistry (1997), 40(22), 3659-3669
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Analogs of estradiol-17β (E2) have been evaluated for estrogen receptor (ER) binding affinity and mitogenic potential in the human breast cancer cell line MCF-7. These 42 compds. represent subtle modifications of the natural estrogen structure through the placement of hydroxyl, amino, nitro, or iodo groups around the ring system in addition to, or as replacement of, the 3- and 17β-hydroxyls of E2. The mitogenic activity of the analogs was found to be related to ER binding only to a limited extent. To elucidate structural features that are uniquely responsible for receptor binding affinity or mitogen potential of estrogens, the three-dimensional quant. structure-activity (QSAR) method Comparative Mol. Field Anal. (CoMFA) was employed. Sep. CoMFA models for receptor binding and cell growth stimulation were optimized through the use of various alignment rules and region step size. Whereas the CoMFA contour plots did outline the shared structural requirements for the two measured biol. properties, specific topol. features in this set of estrogens were delineated that distinguish mitogenic potential from ER binding ability. In particular, steric interference zones which affected growth extend in a band from above the A-ring to position 4 and below, whereas the ER binding steric interference zones are limited to isolated polyhedra in the 1,2 and 4 positions and the α face of the B-ring. In addition, electroneg. features located around the A-, B-, or C-rings contribute to receptor affinity. However, growth is dependent only on electroneg. and electropos. properties near the 3-position. In a final QSAR model for the mitogenic response, the value of ER binding was included along with structural features as a descriptor in CoMFA. The resulting 3D-QSAR has the most predictive potential of the models in this study and can be considered a prototype model for the general evaluation of a steroidal estrogen's growth stimulating ability in MCF-7 cells. For example, the location of D-ring contours illustrate the model's preference for 17β-hydroxy steroids over the less mitogenic 17α- and 16α-hydroxy compds. In addition, the enhanced mitogenic effect of steric bulk in the 11α-position is also evident. The QSAR studies in this report illustrate the fact that while ER binding may be a required factor of the estrogen dependent growth response in MCF-7 cells, particular structural characteristics, in addition to those responsible for tight receptor binding, must be present to induce an optimal mitogenic response. Therefore, this report demonstrates that the CoMFA QSAR method can be utilized to characterize structural features of test compds. that account for different types of estrogenic responses.

CC 2-2 (Mammalian Hormones)
REFERENCE COUNT: 61 THERE ARE 61 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 15 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:478454 CAPLUS
DOCUMENT NUMBER: 127:144867
TITLE: Treatment of human prostate tumors PC-3 and TSU-PR1 with standard and investigational agents in SCID mice
AUTHOR(S): **Polin, Lisa**; Valeriote, Frederick; White, Kathryn; Panchapor, Chiab; Pugh, Susan; Knight, Juiwanna; Lorusso, Patricia; Hussain, Maha; Liversidge, Elaine; Peltier, Nancy; Golakoti, Trimurtulu; Patterson, Gregory; Moore, Richard; **Corbett, Thomas H.**
CORPORATE SOURCE: Division of Hematology and Oncology, Department of Internal Medicine, Wayne State University School of Medicine, Detroit, USA
SOURCE: Investigational New Drugs (1997), 15(2), 99-108
CODEN: INNDDK; ISSN: 0167-6997
PUBLISHER: Kluwer
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Both the PC-3 and the TSU-PR1 prostate tumor models were found to be satisfactory for chemotherapeutic investigations in ICR-SCID mice. The 30 to 60 mg fragments implanted took in all mice (as judged by 100% takes in the controls of all expts. as well as the passage mice). The tumor volume doubling time was 4.0 days for PC-3 and 2.5 days for TSU-PR1. Nine agents were evaluated IV against early stage s.c. PC-3 tumors, with Nano-piposulfan being the only agent highly active (4.9 log kill). Three other agents were moderately active: Taxol (1.5 log kill), Cryptophycin-8 (1.6 log kill), Vinblastine (1.0 log kill). Five agents were inactive: VP-16, Adriamycin, CisDDPt, 5-FUra, and **Cyclophosphamide**. Ten agents were evaluated IV against early stage s.c. TSU-PR1 tumors. Three agents were highly active, producing >6 log kill and curses: Taxol (5/5 cures), Cryptophycin-8 (5/5 cures), Vinblastine (2/4 cures). Two other agents were moderately active: Nano-piposulfan (1.2 log kill), and **Cyclophosphamide** (1.1 log kill). Five agents were inactive: VP-16, Adriamycin, CisDDPt, 5-FUra, and BCNU. In part, activity was determined by the ability of the SCID mice to tolerate meaningful dosages of the agents. Agents producing granulocyte toxicity (e.g., Adriamycin) were poorly tolerated and appeared less active than expected. Vinblastine, producing little or no granulocyte toxicity was very well tolerated and appeared to be more active than expected.
CC 1-6 (Pharmacology)
IT 50-18-0, **Cyclophosphamide** 51-21-8, 5-Fluorouracil 154-93-8, BCNU 865-21-4, Vinblastine 2608-24-4, Piposulfan 15663-27-1, Cisplatin 25316-40-9, Adriamycin 33069-62-4, Taxol 33419-42-0, VP-16 168482-36-8, Cryptophycin-8
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prostate cancer treatment with and granulocyte toxicity of standard and investigational antitumor drugs)
REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 16 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:183114 CAPLUS
DOCUMENT NUMBER: 126:233229
TITLE: Preclinical antitumor activity of CI-994
AUTHOR(S): LoRusso, Patricia Mucci; Demchik, Lisa; Foster, Brenda; Knight, Juiwanna; Bissery, Marie-Christine;

Polin, Lisa Marie; Leopold, Wilbur R.,III; **Corbett, Thomas H.**
CORPORATE SOURCE: Division of Hematology/Oncology, Department of Internal Medicine, Harper Hospital, Wayne State University, Detroit, MI, 48201, USA
SOURCE: Investigational New Drugs (1996), 14(4), 349-356
CODEN: INNDDK; ISSN: 0167-6997
PUBLISHER: Kluwer
DOCUMENT TYPE: Journal
LANGUAGE: English
AB CI-994 [aka: acetyldinaline; PD 123654; 4-acetylamino-N-(2'aminophenyl)-**benzamide**] (Figure 1) is a novel antitumor agent with a unique mechanism of action. It is the acetylated metabolite of dinaline, a compound previously identified as having cytotoxic and cytostatic activity against several murine and human xenograft tumor models. CI-994 had activity against 8/8 solid tumors tested (log cell kills at the highest non-toxic dose): pancreatic ductal adenocarcinoma #02 (4.7); pancreatic adenocarcinoma #03 (3.0; 1/6 cures); colon adenocarcinoma #38 (1.6); colon adenocarcinoma #51/A (1.1); mammary adenocarcinoma #25 (1.7); mammary adenocarcinoma #17/ADR (0.5); Dunning osteogenic sarcoma (4.0); and the human prostate carcinoma LNCaP (1.2). CI-994 had the same spectrum of activity in vivo as dinaline. It also behaved similarly in schedule comparison/toxicity trials. Prolonged administration with lower drug doses was more effective than short-term therapy at higher individual doses. If doses were kept between 40 and 60 mg/kg/injection, prolonged administration (> 50 days) was tolerated with no gross toxicity. Doses ≥ 90 mg/kg/injection caused lethality after 4-5 days of administration. The maximum tolerated total dose was also increased with smaller individual doses administered for prolonged intervals. Clin. Phase I trials are ongoing with this agent.
CC 1-6 (Pharmacology)

L17 ANSWER 17 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:154456 CAPLUS
DOCUMENT NUMBER: 126:194980
TITLE: Preclinical anticancer activity of cryptophycin-8
AUTHOR(S): **Corbett, T. H.**; Valeriote, F. A.; Demchik, L.; **Polin, L.**; Panchapor, C.; Pugh, S.; White, K.; Knight, J.; Jones, J.; et al.
CORPORATE SOURCE: Division of Hematology and Oncology, Department of Internal Medicine, Wayne State University School of Medicine, Detroit, MI, 48201, USA
SOURCE: Journal of Experimental Therapeutics & Oncology (1996), 1(2), 95-108
CODEN: JETOFX; ISSN: 1359-4117
PUBLISHER: Rapid Science Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Cryptophycin-8 was prepared by the conversion of the epoxide group on cryptophycin-1 to a chlorohydrin. In the studies reported here, cryptophycin-8 was evaluated for preclin. activity against s.c. tumors of both mouse and human origin. At the highest non-toxic single course treatment, the following results were obtained (Table A). Cryptophycin-8 was less potent than cryptophycin-1 by approx. 4-fold; however, it was both more water soluble and had greater therapeutic efficacy, as demonstrated by %T/C, tumor cell log kill values, range of dose effectiveness and host cures.
CC 1-6 (Pharmacology)

L17 ANSWER 18 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1996:688059 CAPLUS
DOCUMENT NUMBER: 126:14862
TITLE: Crystal structure, receptor binding, and gene regulation of 2- and 4-nitroestradiols
AUTHOR(S): **Palomino, Eduardo**; Heeg, Mary Jane; Pilat, M. J.; Hafner, M.; **Polin, L.**; Brooks, S. C.
CORPORATE SOURCE: Dep. Chem. Biochem., Walker Cancer Res. Inst., Wayne State Univ., Detorit, MI, USA
SOURCE: Steroids (1996), 61(11), 670-676
CODEN: STEDAM; ISSN: 0039-128X
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Crystal structures of 2-nitroestradiol and 4-nitroestradiol showed two different mol. conformations for each compound The crystal structure of 4-nitroestradiol, as well as that of 4-nitroestrone 3-Me ether, displayed a nitro group in which the oxygens were perpendicular to the aromatic ring and were thus nonconjugating. On the other hand, the nitro-oxygens in 2-nitroestradiol were periplanar, with the aromatic ring permitting conjugation. This latter structure bound to estrogen receptors with 1/1000th the affinity of estradiol and was inefficient in gene stimulation. 4-Nitroestradiol possessed a relative binding affinity 40-fold greater than that of the 2-nitro derivative and actively induced responsive genes at a concentration of 10-8 M. Whereas binding affinity can be explained primarily by polar groups and skeletal structure, gene induction may be linked to electronic induction in ring A that causes a requisite electroneg. isopotential around the mol. This electroneg. characteristic also produces conformational changes in the alicyclic backbone of the estrogen, specially ring B, which could interfere with the mol. fit of the nitroestradiols with estrogen receptor.
CC 2-2 (Mammalian Hormones)
Section cross-reference(s): 32

L17 ANSWER 19 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1996:550995 CAPLUS
DOCUMENT NUMBER: 125:265327
TITLE: Identification and antitumor activity of a reduction product in the murine metabolism of pyrazoloacridine (NSC-366140)
AUTHOR(S): **Palomino, Eduardo**; Foster, Brenda; Kempff, Maya; **Corbett, Thomas**; Wiegand, Richard; **Horwitz, Jerome**; Baker, Laurence
CORPORATE SOURCE: Walker Cancer Research Inst., Detroit, MI, 48201, USA
SOURCE: Cancer Chemotherapy and Pharmacology (1996), 38(5), 453-458
CODEN: CCPHDZ; ISSN: 0344-5704
PUBLISHER: Springer
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The involvement of the nitro group functionality in pyrazoloacridine (NSC-366140) (I), an anticancer agent, and the metabolites of I was investigated. Urine and stool samples were collected from mice before and after I treatment, and evaluated by MS. One of the characterized metabolite was synthesized and tested in vitro and in vivo for anticancer activity. One major fraction from mouse stool was initially characterized by MS as the 5-aminopyrazoloacridine (II). II was chemical synthesized by catalytic hydrogenation of I and was marginally cytotoxic in vitro and inactive in vivo against a tumor cured by I. The inactivity of chemical

generated II does not provide conclusive evidence that this pathway is not involved in the cytotoxicity of I because other intermediates in the nitro reduction pathway may have a role in the activity of I.
CC 1-6 (Pharmacology)

L17 ANSWER 20 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1996:276635 CAPLUS
DOCUMENT NUMBER: 124:331942
TITLE: Comparative efficacy of DMP 840 against mouse and human solid tumor models
AUTHOR(S): LoRusso, Patricia; Demchik, Lisa; Dan, Maria; **Polin, Lisa**; Gross, Janet L.; **Corbett, Thomas H.**
CORPORATE SOURCE: Harper Hospital, Wayne State University, Detroit, MI, 48201, USA
SOURCE: Investigational New Drugs (1995), 13(3), 195-203
CODEN: INNDDK; ISSN: 0167-6997
PUBLISHER: Kluwer
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Background:. DMP 840 is a compound from a class of bis-naphthalimide antitumor agents that recently completed Phase I clin. trials at three North American centers and is currently undergoing Phase II testing. Preclinically, it was shown to have curative activity against a variety of human tumor xenograft models. Purpose:. To test DMP 840 both in vitro and in vivo for antiproliferative activity against predominantly mouse tumor models. Methods:. A disk diffusion soft agar colony formation assay was used to determine the in vitro growth inhibitory activity against a selection of mouse and human tumor cell lines, and the comparable selective mouse solid tumors were used for in vivo testing. Result:. In vitro DMP 840 exhibited equal cytotoxicity for human tumors (including MX-1 directly cultured from nude mice), mouse tumors and normal cells. In vivo DMP 840 was only modestly active or inactive against the following mouse tumors: Mam 16/C, T/C = 30% (T/C = Percent Tumor Growth Inhibition); Mam 16/C/ADR, T/C = 33%; Colon 38, T/C = 9%; Panc 03, T/C = 53%; Colon 51/A, T/C = 28%; Panc 02, T/C = 52%; P388/0, 36% ILS (Percent Increased Life Span) and P388/ADR, 14% ILS. Furthermore, the antitumor activity was only observed at the highest non-toxic dose and was associated with a large body
weight loss. In contrast, the agent was highly active against the human breast tumor MX-1 implanted s.c. in either athymic nude or SCID mice (Nudes: T/C = 0%; 1/5 cures; SCIDS: T/C = 0%; 5/5 cures). Conclusions:. Although there was no selective cytotoxicity in our clonogenic assay for human vs. mouse tumor cell lines, selective activity in vivo for human xenograft tumors was noted. Overall, this compound is rather unique in its differential degree of in vivo activity for human vs. mouse tumors. Implications:. Phase II trials, which are ongoing, will help determine if the preclin. in vivo selective activity of DMP 840 translates to clin. activity in man.
CC 1-6 (Pharmacology)

L17 ANSWER 21 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1996:43751 CAPLUS
DOCUMENT NUMBER: 124:134457
TITLE: Tumor models and the discovery and secondary evaluation of solid tumor active agents
AUTHOR(S): **Corbett, Thomas**; Valeriote, Fred; LoRusso, Patricia; **Polin, Lisa**; Panchapor, Chiab; Pugh, Susan; White, Kathryn; Knight, Juiwanna;

Demchik, Lisa
CORPORATE SOURCE: School of Medicine, Wayne State University, Detroit, MI, 48201, USA
SOURCE: International Journal of Pharmacognosy (1995), 33(Suppl., Drug Discovery and Development), 102-22
CODEN: IJPYEW; ISSN: 0925-1618
PUBLISHER: Swets & Zeitlinger
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review, with over 30 refs. Each independently arising tumor is a sep. and unique biol. entity with its own unique histol. appearance, biol. behavior, and drug response profile. Thus, in drug discovery, no single tumor has been a perfect predictor for any other tumor. For this reason, new agents are evaluated in a variety of tumor models which is known as breadth of activity testing. In recent years, human tumors implanted in athymic nude mice and SCID mice have also become available for breadth of activity testing. In studies carried out in these labs., it was found that 10 human tumors metastasized in the SCID mice, but failed to metastasize in nude mice. In addition, tumor growth and tumor takes were superior in the SCID mice. The strengths and weaknesses of xenograft model systems are discussed. For example, most human tumor xenograft models are excessively sensitive to alkylating agents as well as to a new class of DNA binders (XE840 and XP315). Using human tumor models that are the least sensitive to these classes of agents is suggested. A drug discovery screen using a disk-diffusion-soft-agar-colony formation assay is presented. This assay employs leukemia cells, normal cells, and cells from solid tumors of mouse and human origin. The goal is to find agents with greater cytotoxicity for solid tumor cells than for leukemic or normal cells. Over 50,000 materials of synthetic and natural product origin have been tested in this disk-assay which identified a variety of agents. In-vivo breadth of activity testing is presented for several agents that fit the desired cellular selectivity in-vitro. Three of these agents are currently in Phase-1,2 clin. trials [PZA (NSC366140), Acetyldinaline (CI994), and WIN33377]. Three others are in clin. development (XK469, Nanoparticle-Piposulfan, and Cryptophycin-8). All of these agents are highly active and broadly active against a variety of solid tumors.
CC 1-0 (Pharmacology)

L17 ANSWER 22 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1995:359096 CAPLUS
DOCUMENT NUMBER: 122:229818
TITLE: Antitumor activity of N-[[1-[[2-(diethylamino)ethyl]amino]-9-oxo-9H-thioxanthen-4-yl]methyl]**methanesulfonamide** (WIN33377) and analogs
AUTHOR(S): **Corbett, Thomas**; Lowichik, Nancy; Pugh, Susan; **Polin, Lisa**; Panchapor, Chiab; White, Kathryn; Knight, Juiwanna; Demchik, Lisa; Jones, Julie; et al.
CORPORATE SOURCE: Harper Hospital, Wayne State University, Detroit, MI, 48202, USA
SOURCE: Expert Opinion on Investigational Drugs (1994), 3(12), 1281-92
CODEN: EOIDER; ISSN: 0967-8298
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 23 refs. WIN33377 (Sterling/Kodak) entered Phase I clin. trials in 1994. The dose-limiting toxicity has not been reached with

completion of the 225 mg/m2 level, Q28 day schedule. To date, the agent has been very well tolerated with no evidence of liver toxicity. Eventually, a weekly schedule will be undertaken, which is consistent with the rapid host recovery time for this agent (six days). WIN33377 is an analog of Hycanthone, an antischistosomal agent, that also has antitumor activity in preclin. models. However, Hycanthone is very poorly tolerated at the efficacious dose levels. Clin. trials of Hycanthone were carried out between 1978 and 1983, producing severe liver toxicity with drug induced deaths. No antitumor activity was recorded. WIN33377 and a variety of analogs were discovered to have markedly improved antitumor activity, and were well tolerated in mice. Most analogs had no evidence of liver toxicity with WIN33377 being totally devoid of liver toxicity. The key to better efficacy and toxicity was the replacement of a -CH2OH functional group in the 4-position of the mol. with a -CH2NR1R2 group (an oxygen to a nitrogen). Structure-activity relationships in vitro and in vivo are discussed for the series of WIN33377 analogs.

CC 1-0 (Pharmacology)

ST review **thioxanthenylmethanesulfonamide** WIN33377 analog antitumor structure

IT Neoplasm inhibitors
(antitumor activity of (diethylamino)**ethylaminothioxanthenylmethyl methanesulfonamide** (WIN33377) and its analogs)

IT Molecular structure-biological activity relationship
(neoplasm-inhibiting, antitumor activity of (diethylamino) **ethylaminothioxanthenylmethylmethanesulfonamide** (WIN33377) and its analogs)

IT 146537-07-7, Win 33377
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antitumor activity of (diethylamino)**ethylaminothioxanthenylmethyl methanesulfonamide** (WIN33377) and its analogs)

L17 ANSWER 23 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1994:525485 CAPLUS
DOCUMENT NUMBER: 121:125485
TITLE: Skeletal conformations and receptor binding of some 9,11-modified estradiols
AUTHOR(S): **Palomino, Eduardo**; Heeg, Mary Jane; **Horwitz, Jerome P.**; **Polin, L.**; Brooks, S. C.
CORPORATE SOURCE: Walker Cancer Research Institute, Wayne State University, Detroit, MI, 48201, USA
SOURCE: Journal of Steroid Biochemistry and Molecular Biology (1994), 50(1-2), 75-84
CODEN: JSBBEZ; ISSN: 0960-0760
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effect of the modification of the 9-11 positions on the skeletal conformation of estradiol (E2) has been analyzed by x-ray crystallog. and MM2 mol. mechanics. The 11β-hydroxyl and 11-keto analogs of E2 maintained ring conformations which were similar to the natural hormone (E2). Introduction of a double bond at position 9-11 induced a flattening of the entire steroid mol. An 11α-hydroxyl group brought about significant changes in the alicyclic rings of E2. 9β-Estradiol and 11-keto-9β-estradiol formed ring conformations which were significantly bent from E2 (below the plane of the A-ring). Examination of the affinity of these C-ring analogs of E2 for the human estrogen receptor has shown extreme variations. A hydroxyl group placed either α or

β at the 11-position yielded ligands with vastly different and reduced affinities for the receptor. The low affinity of 11α-hydroxyestradiol (1/300th of E2) may be due to the drastic structural change induced in the alicyclic portion of the mol., as well as, to the steric or electrostatic effects of the α-hydroxyl group upon the receptor protein. An 11β-hydroxyl group diminished the receptor binding to 1/60th that of E2 without alicyclic ring distortions, whereas a 9-11 unsatn. reduced the binding to 1/5th although this steroid displayed a flattening of rings B, C, and D. The 11-keto function, which had little effect on the conformation of the estrogen nucleus, reduced the affinity of this ligand to 1/1000th that of E2. The neg. bend at the C-ring of 11-keto-9β-estradiol and 9β-estradiol prevented these ligands from binding receptor. Some of the observed receptor interactions were related to structural alterations in the estrogen ring system induced by modifications on the 9-11 region.

CC 2-2 (Mammalian Hormones)

L17 ANSWER 24 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1994:315145 CAPLUS
DOCUMENT NUMBER: 120:315145
TITLE: Comparative Molecular Field Analysis of the Antitumor Activity of 9H-Thiioxanthen-9-one Derivatives against Pancreatic Ductal Carcinoma 03
AUTHOR(S): **Horwitz, Jerome P.**; Massova, Irina; Wiese, Thomas E.; Besler, Brent H.; **Corbett, Thomas H.**
CORPORATE SOURCE: School of Medicine, Wayne State University, Detroit, MI, 48201, USA
SOURCE: Journal of Medicinal Chemistry (1994), 37(6), 781-6
CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The present study establishes correlations of in vivo growth inhibition of a solid tumor, pancreatic ductal adenocarcinoma (Panc 03), of mice with the steric and electrostatic fields and the hydrophobic parameter log P of a series (32) of 1-[[2-(dialkylamino)alkyl]amino]-9H-thioxanthen-9-ones by the 3D-QSAR method comparative mol. field anal. (CoMFA). The template mol. model was hycanthone methanesulfonate, the structure of which had been established previously by X-ray crystallog. The hycanthone base is protonated at the terminal nitrogen N(2), and an intramol. hydrogen bond is present between the proximal nitrogen N(1) and carbonyl oxygen O(1) atoms. Crystallog. data also indicate a planar arrangement of bonds around N(1). However, the mol. geometry of hycanthone methanesulfonate, optimized by semiempirical MO methods (PM3, MNDO, AM1), showed the expected trigonal-**pyramidal** configuration for N(1). A comparison of MO and ab initio methods applied to a model compound, 1-amino-9H-thioxanthen-9-one, led to the selection of PM3 as the method for full geometry optimization of first the cationic and then the neutral forms of 32 compds. studied, whereas AM1 provided atomic charges for these same structures save those incorporating a **sulfonamide** moiety. Acceptable values for the latter were obtained from ab initio calcns. Structures were aligned by minimizing root-mean-square (rms) differences in the fitting of structures of hycanthone methanesulfonate using the FIT option of SYBYL. An alternative strategy of alignment, steric and electrostatic alignment (SEAL), was invoked to provide a comparison of statistical data generated with the rms alignment. The rms-fit alignment of structures produced slightly better cross-validated and conventional r2 values than those generated with the SEAL method. In addition, the rms-fit data indicate that a shift in the lattice of one-half of its spacing has a

much smaller effect on the CoMFA data for a lattice of 1 Å than one of 2 Å. Inclusion of log P in a CoMFA of the neutral structures effected a small (ca. 8-10%) but significant improvement in cross-validated r2 values. The relative contributions of the hydrophobic effects and the steric and electrostatic fields to the conventional r2 values were 16%, 42%, and 42%, resp. By contrast, incorporation of frontier MO (HOMO and LUMO) energies or their gaps in the PLS analyses failed to enhance correlation coeffs. derived for either the charged or uncharged compds. Graphical results of the non-cross-validated CoMFA studies of the cationic structures are shown in the form of three-dimensional coefficient contour maps that delineate the steric and electrostatic features of the model. Maps of the electrostatic field indicate areas where pos. or neg. interactions favor tumor-growth inhibition. The present findings indicate, in accord with the rationale for CoMFA, that the interactions, which seem most appropriate for describing the anticancer activities of the 9H-thioxanthen-9-one derivs., are noncovalent.

CC 1-3 (Pharmacology)

L17 ANSWER 25 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN

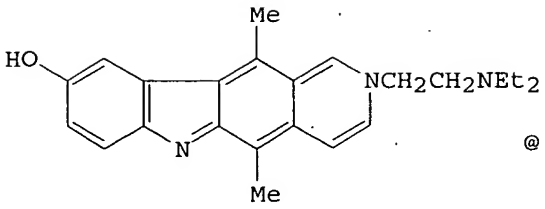
ACCESSION NUMBER: 1993:640920 CAPLUS
DOCUMENT NUMBER: 119:240920
TITLE: Comparative molecular field analysis of in vitro growth inhibition of L1210 and HCT-8 cells by some pyrazoloacridines
AUTHOR(S): **Horwitz, Jerome P.**; Massova, Irina; Wiese, Thomas E.; Wozniak, Antoinette J.; **Corbett, Thomas H.**; Sebolt-Leopold, Judith S.; Capps, David B.; Leopold, Wilbur R.
CORPORATE SOURCE: Sch. Med., Wayne State Univ., Detroit, MI, 48202, USA
SOURCE: Journal of Medicinal Chemistry (1993), 36(23), 3511-16
CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In vitro screening of a number of 2-(aminoalkyl)-5-nitropyrazolo[3,4,5-kl]acridines has previously indicated (Sebolt, et al. 1987) that these compds., in general, exhibit selective cytotoxicity against the human colon adenocarcinoma, HCT-8, cell line, relative to mouse leukemia L1210 cells. Comparative mol. field anal. (CoMFA) was applied to HCT-8 and L1210 growth inhibition assays (IC50s) of a series (44) of the pyrazoloacridine derivs. with the objective of predicting improved solid tumor selectivity. In the absence of crystallog. data, the 9-methoxy derivative, which is currently in clin. study, was selected as the template mol. model. Two different structural alignments were tested: an alignment of structures based on root mean square (RMS)-fitting of each structure to the 9-methoxy derivative was compared with an alternative strategy, steric and electrostatic alignment (SEAL). Somewhat better predictive cross-validation correlations (r2) were obtained with models based on RMS vis-a-vis SEAL alignment for both sets of assays. A large change in lattice spacing, e.g., 2 to 1 Å, causes significant variations in the CoMFA results. A shift in the lattice of half of its spacing had a much smaller effect on the CoMFA data for a lattice of 1 Å than one of 2 Å. The relative contribution of steric and electrostatic fields to both models were about equal, underscoring the importance of both terms. Neither calculated log P nor HOMO and/or LUMO energies contribute to the model. Steric and electrostatic fields of the pyrazoloacridines are the sole relevant descriptors to the structure-activity (cross-validated and conventional) correlations obtained with the cytotoxic data for both the L1210 and HCT-8 cell lines. The cross-validated r2, derived from partial least-squares calcns., indicated considerable predictive capacity for

growth inhibition of both the leukemia and solid-tumor data. Evidence for the predictive performance of the CoMFA-derived models is provided in the form of plots of actual vs predicted growth inhibition of L1210 and HCT-8 cells, resp., by the pyrazoloacridines. The steric and electrostatic features of the QSAR are presented in the form of standard deviation coefficient
contour maps of steric and electrostatic fields. The maps indicate that increases or decreases in steric bulk that would enhance growth inhibition of HCT-8 cells would likewise promote growth inhibition of L1210 cells. Contour maps generated to analyze the electrostatic field contributions of the pyrazoloacridines to growth inhibition provided an essentially similar set of results. It is apparent that steric and electrostatic fields alone are inadequate in the CoMFA to characterize the in vitro solid tumor selectivity of the pyrazoloacridines. This points to a need to supplement the cytotoxic data with results of further study that focuses on a quant. comparison of the potential for differential metabolic activation of the pyrazoloacridines in the two cell lines.
CC 1-3 (Pharmacology)

L17 ANSWER 26 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1993:45609 CAPLUS
DOCUMENT NUMBER: 118:45609
TITLE: A dihydropyridine carrier system for delivery of 2',3'-dideoxycytidine (DDC) to the brain
AUTHOR(S): **Palomino, Eduardo**; Kessel, David; **Horwitz, Jerome P.**
CORPORATE SOURCE: Michigan Cancer Found., Detroit, MI, 48202, USA
SOURCE: Nucleosides & Nucleotides (1992), 11(9), 1639-49
CODEN: NUNUD5; ISSN: 0732-8311
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The present study extends the dihydropyridine .dblarw. pyridinium salt redox system to the delivery and sustained release of 2',3'-dideoxycytidine (DDC) in the brain of mice in a continuing search for agents that may prove effective in reversing complicating neurol. disorders of AIDS.
CC 63-5 (Pharmaceuticals)
Section cross-reference(s): 1, 28

L17 ANSWER 27 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1991:220847 CAPLUS
DOCUMENT NUMBER: 114:220847
TITLE: Activity of datelliptium acetate (NSC 311152; SR 95156A) against solid tumors of mice
AUTHOR(S): Mucci-LoRusso, Patricia; **Polin, Lisa**; Biernat, Laura A.; Valeriote, Frederick A.; **Corbett, Thomas H.**
CORPORATE SOURCE: Sch. Med., Wayne State Univ., Detroit, MI, 48201, USA
SOURCE: Investigational New Drugs (1990), 8(3), 253-61
CODEN: INNDDK; ISSN: 0167-6997
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



@ HOAc

I

AB Datelliptium acetate (NSC 311152) (I) is a water soluble ellipticine analog. I is a solid tumor-selective compound In vitro, in a disk-diffusion, soft-agar colony-formation assay (25 μg/disk), I demonstrated solid tumor selectivity (compared to leukemia L1210) against colon adenocarcinoma 38 and pancreas ductal carcinoma 03. Upon i.v. administration, I was effective in vivo against a variety of murine solid tumors. Responses at maximum tolerated doses were: colon number 07/A (T/C = 33%); 0.60 log cell kill), number 38 (T/C = 0%; 4.2 log cell kill), colon number 51/A (T/C = 2%; 1.2 log cell kill), undifferentiated colon number 26/A (T/C = 38%; 0.4 log kill), mammary number 16/C (T/C = 10%; 1.7 log cell kill), and pancreatic ductal carcinoma number 03 (T/C = 0%; 80% cures through day 38). I was ineffective against pancreas number 02 (T/C = 45%), mammary 17/A (T/C = 53%), and 17/A/ADR (T/C = 52%). At efficacious doses acute neurotoxicity (i.e. stupor and lethargy) and weight loss were noted (with rapid recovery from both toxicities). There were no delayed toxicities. I was slightly necrotizing and produced pain on s.c. injections.

CC 1-6 (Pharmacology)

L17 ANSWER 28 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1990:604541 CAPLUS

DOCUMENT NUMBER: 113:204541

TITLE: Antitumor efficacy of interleukin-2 alone and in combination with adriamycin and dacarbazine in murine solid tumor systems

AUTHOR(S): LoRusso, Patricia Mucci; Aukerman, Sharon Lea; **Polin, Lisa**; Redman, Bruce G.; Valdivieso, Manuel; Biernat, Laura; **Corbett, Thomas H.**

CORPORATE SOURCE: Sch. Med., Wayne State Univ., Detroit, MI, 48202-0188, USA

SOURCE: Cancer Research (1990), 50(18), 5876-82
CODEN: CNREA8; ISSN: 0008-5472

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Recombinant interleukin-2 (IL-2/chemotherapy combinations have recently entered clin. trial. The rationale for sequencing has primarily been empiric or based on in vitro data. To establish in vivo models for chemoimmunotherapy trials, the authors investigated IL-2 alone and in combination with dacarbazine (DTIC) and adriamycin. IL-2 (as a single agent given i.v. at 1-3 + 105 Cetus units once daily for 5 days, repeated 7-10 days later), was highly active against an immunogenic line of colon adenocarcinoma number 11/A [tumor growth inhibition (T/C) = 0% with cures]. It was modestly active against colon adenocarcinoma number 38 (T/C = 39%), mammary adenocarcinoma number 16/C (T/C = 18%), and B16 melanoma (T/C = 21%). IL-2 was inactive against colon adenocarcinoma number 7/A (T/C = 83%). Combination trials were done using DTIC and IL-2 against colon number 7/A and upstaged colon number 11/A. The combination of adriamycin and IL-2 was tested against mammary adenocarcinoma number 16/C. In the DTIC/IL-2 combination trials, the combination was superior over either agent used

alone. In the IL-2/adriamycin trials, the combination was no better than adriamycin alone at optimum dosages.
CC 1-6 (Pharmacology)
Section cross-reference(s): 15

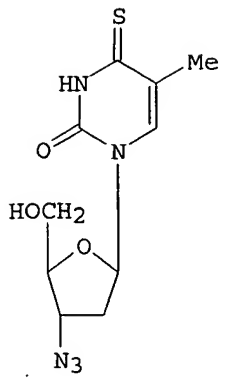
L17 ANSWER 29 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1990:544999 CAPLUS
DOCUMENT NUMBER: 113:144999
TITLE: Antitumor efficacy of PD115934 (NSC 366140) against solid tumors of mice
AUTHOR(S): LoRusso, Patricia; Wozniak, Antoinette J.; **Polin, Lisa**; Capps, David; Leopold, Wilbur R.; Werbel, Lester M.; Biernat, Laura; Dan, Maria E.; **Corbett, Thomas H.**
CORPORATE SOURCE: Sch. Med., Wayne State Univ., Detroit, MI, 48202-0188, USA
SOURCE: Cancer Research (1990), 50(16), 4900-5
CODEN: CNREA8; ISSN: 0008-5472
DOCUMENT TYPE: Journal
LANGUAGE: English
AB PD115934 is a soluble pyrazoloacridine derivative with both human and murine solid tumor selectivity in vitro in a soft agar disk diffusion assay, relative to its activity against murine L1210 leukemia. In mice it was highly active against solid colon adenocarcinoma 38 and pancreas ductal carcinoma 03, which was consistent with the cellular cytotoxicity seen in the disk diffusion assay. A log cell kill of >4.0 was demonstrated in vivo in both models. PD115934 was administered by both bolus and infusion. It was a schedule-independent agent with peak plasma level toxicity. The main toxicity encountered with infusion therapy was myelosuppression. With bolus therapy, central nervous system toxicities were dose-limiting. A 2-h infusion twice weekly in humans is recommended to obtain a total dose of 360 mg/m2 over 8 wk.
CC 1-6 (Pharmacology)

L17 ANSWER 30 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1990:192065 CAPLUS
DOCUMENT NUMBER: 112:192065
TITLE: Binding, x-ray and NMR studies of the three A-ring isomers of natural estradiol
AUTHOR(S): **Palomino, Eduardo**; Heeg, Mary Jane; **Horwitz, Jerome P.**; Brooks, Sam C.
CORPORATE SOURCE: Michigan Cancer Found., Detroit, MI, 48201, USA
SOURCE: Journal of Steroid Biochemistry (1990), 35(2), 219-29
CODEN: JSTBBK; ISSN: 0022-4731
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 112:192065
AB The effect of the position of the phenolic hydroxyl on the conformations of the 3 A-ring isomers of estradiol (E2), namely, estra-1,3,5(10)-trien-1,17β-diol, estra-1,3,5(10)-trien-2,17β-diol, and estra-1,3,5(10)-trien-4,17β-diol, has been analyzed by X-ray crystallog. The results of these analyses were correlated with the absorptions of the angular Me groups in the [1H]NMR spectra of these isomers and natural E2. The changes in chemical shift of protons at C18 corresponded to skeletal modifications in the steroid structure which changed the anisotropic effect of the hydroxyl group at C17. Examination of the affinity of these A-ring isomers of E2 for the estrogen receptor has shown the 2-hydroxylated isomer to retain 1/5th the affinity of E2 for its binding protein. The 1- and 4-hydroxylated derivs. bound to a much lesser

extent. The receptor affinities of these estrogen analogs may be related to the angle between the 18-Me and the 17β-hydroxyl groups (or the dihedral angle between the planar A-ring and the angular C18 methyl), as well as the position of the A-ring hydroxyl group.
CC 2-2 (Mammalian Hormones)

L17 ANSWER 31 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1990:48411 CAPLUS
DOCUMENT NUMBER: 112:48411
TITLE: Activity of batracylin (NSC-320846) against solid tumors of mice
AUTHOR(S): Mucci-LoRusso, Patricia; **Polin, Lisa**; Bissery, Marie Christine; Valeriote, Frederick; Plowman, Jacqueline; Luk, Gordon D.; **Corbett, Thomas H.**
CORPORATE SOURCE: Sch. Med., Wayne State Univ., Detroit, MI, 48201, USA
SOURCE: Investigational New Drugs (1989), 7(4), 295-306
CODEN: INNDDK; ISSN: 0167-6997
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Batracylin is a water insol. antitumor agent both active orally and i.p. against colon adenocarcinomas. In a disk diffusion soft agar colony formation assay batracylin was active against colon adenocarcinoma and pancreas ductal carcinoma. In vivo batracylin given orally or s.c. was active against mammary adenocarcinoma colon adenocarcinoma, pancreas ductal carcinoma, and hepatoma. At efficacious doses, delayed neurotoxicity, hepatic toxicity, and a weight loss were noted. Batracylin had low activity against L1210 leukemia cells. Although showing activity against selected murine solid tumors, it lacked curative potential with early stage disease and has shown relative inactivity in vitro against human solid tumor cell lines.
CC 1-6 (Pharmacology)

L17 ANSWER 32 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1990:36355 CAPLUS
DOCUMENT NUMBER: 112:36355
TITLE: Synthesis and in vitro evaluation of some modified 4-thiopyrimidine nucleosides for prevention or reversal of AIDS - associated neurological disorders
AUTHOR(S): **Palomino, Eduardo**; Meltsner, Bernard R.; Kessel, David; **Horwitz, Jerome P.**
CORPORATE SOURCE: Sch. Med., Wayne State Univ., Detroit, MI, 48201, USA
SOURCE: Journal of Medicinal Chemistry (1990), 33(1), 258-63
CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 112:36355
GI



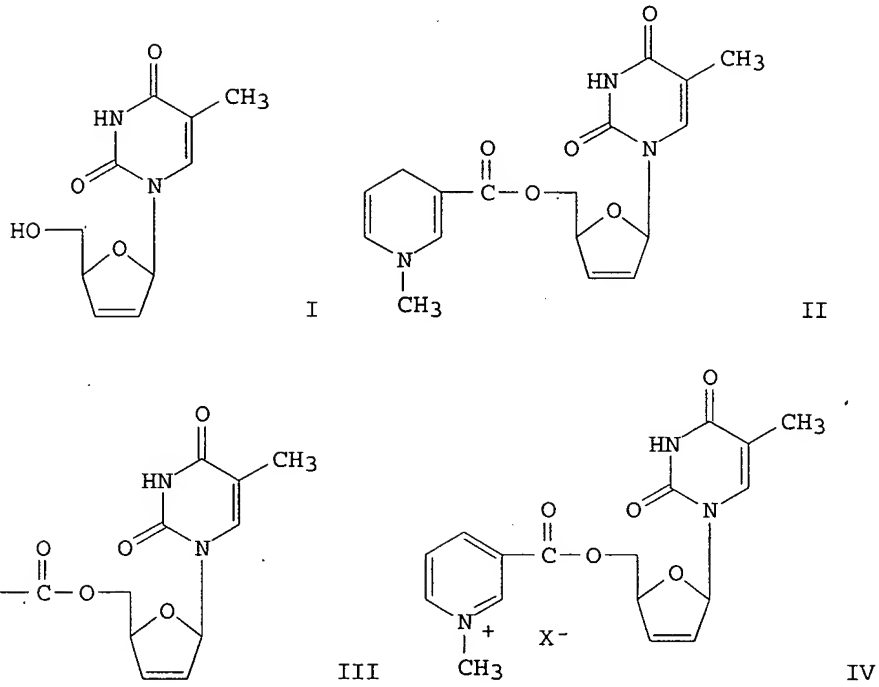
I

AB Oxygen-sulfur exchange at the C-4 carbonyl of several modified pyrimidine nucleosides, including 3'-azido-3'-deoxythymidine (AZT), is described in an effort to enhance the lipophilicity and, thereby, the delivery to the central nervous system of the sulfur analogs without compromising the anti-HIV activities of the parental structures. Preparation of 3'-azido-3'-deoxy-4-thiothymidine (I) proceeded from 4-thiothymidine and utilized the same methodol. developed for the initial synthesis of AZT. Thiation of 2',3'-didehydro-3'-deoxythymidine and 2',3'-didehydro-2',3'-dideoxyuridine was carried out with Lawesson's reagent on the corresponding 5'-O-benzoate esters. The products on alkaline hydrolysis gave 2',3'-didehydro-3'-deoxy-4-thiothymidine and 2',3'-didehydro-2',3'-dideoxy-4-uridine (III). The same series of reactions were applied to the 5'-O-benzoate esters of 2',3'-dideoxyuridine and 3'-deoxythymidine to give 2',3'-dideoxy-4-thiouridine (IV) and 3'-deoxy-4-thiothymidine (V). Characterization of the saturated and unsatd. thionucleosides included mass spectrometric studies. Under electron impact conditions, the thiated analogs gave more intense parent ions than the corresponding oxygen precursors. The lipophilicity of thymidine and the 3'-deoxythymidine derivs. are enhanced significantly, as indicated, by increases in corresponding P values (1-octanol-0.1M sodium phosphate) upon replacement of the 4-carbonyl oxygens by sulfur. II, III, IV, and V were evaluated for their effects on HIV-induced cytopathogenicity of MT-2 and CEM cells. Only II and V were moderately active in protecting both cell lines against the cytolytic effect of HIV. The inhibitory effects of II-V on thymidine phosphorylation by rabbit thymus thymidine kinase were evaluated. Only I showed moderate affinity (Ki = 54 μM) for the enzyme. The generally weak anti-HIV activities of the remaining thio analogs are consistent with correspondingly low susceptibilities to thymidine kinase phosphorylation as estimated from the resp. Ki values of the synthetic nucleosides. However, the phosphorylation of the 5'-monophosphate derivs. to their resp. 5'-triphosphates must also be considered in connection with the weak in vitro anti-HIV effects of these thiated compds.

CC 33-9 (Carbohydrates)
Section cross-reference(s): 1, 15

L17 ANSWER 33 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1989:115257 CAPLUS
DOCUMENT NUMBER: 110:115257
TITLE: A dihydropyridine carrier system for sustained delivery of 2',3'-dideoxynucleosides to the brain
AUTHOR(S): **Palomino, Eduardo**; Kessel, David; **Horwitz, Jerome P.**
CORPORATE SOURCE: Sch. Medicine, Wayne State Univ., Detroit, MI, 48201,

USA
SOURCE: Journal of Medicinal Chemistry (1989), 32(3), 622-5
CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 110:115257
GI



I II III IV

AB The present study evaluates the utility of the dihydropyridine .dblharw. pyridinium salt redox system for the specific delivery and sustained release of a model 2',3'-dideoxynucleotide to the brain of mice as the initial effort in a search for agents that may prove effective in reversing the complicating neurol. disorders of AIDS. The unsatd. nucleoside 2',3'-didehydro-2',3'-dideoxythymidine (I), which is effective in protecting ATH8 cells against the cytopathogenicity of HIV-1, was converted to the corresponding N-methyl-1,4-dihydronicotinate derivative, II, in 3 steps. The 5'-O-nicotinate ester, III, obtained by reaction of I with nicotinoyl chloride, was converted in quant. yield to the N-methylpyridinium salt IV on treatment with MeI in acetone. Reduction of the latter with Na2S2O4 gave II in 50% yield. Pseudo-first-order rate consts. for the oxidation of II to III were obsd.in plasma and in homogenates of mouse liver and brain. None of the chemical delivery system II could be detected in the brain of female BDF/1 mice at 1 h postinjection. The peak level of IV in the brain occurred at 3 h with a half-life of 25 h. Both I and N-methylnicotinic acid were readily identified by HPLC in brain homogenate derived from mice injected (25 mg/kg) with II. TLC showed a low level penetration of mouse brain by I (0.44 μg/g wet tissue) following injection of the corresponding labeled [methyl-3H]-2',3'-unsatd. nucleoside (25 mg/kg). The data indicate that II crosses the blood-brain

barrier to be oxidized by cerebral tissue to the ionic structure IV which is locked therein. The sustained local release of a 2',3'-dideoxynucleoside, such as I, from a chemical delivery system (II) represents a potentially useful approach to the treatment of AIDS dementia complex.
CC 33-9 (Carbohydrates)
Section cross-reference(s): 1

L17 ANSWER 34 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1989:88158 CAPLUS
DOCUMENT NUMBER: 110:88158
TITLE: Chemotherapy of the squamous cell lung cancer LC-12 with 5-fluorouracil, cisplatin, carboplatin or iproplatin combinations
AUTHOR(S): Tapazoglou, Efstathios; **Polin, Lisa**; **Corbett, Thomas H.**; Al-Sarraf, Muhyi
CORPORATE SOURCE: Sch. Med., Wayne State Univ., Detroit, MI, 48201, USA
SOURCE: Investigational New Drugs (1988), 6(4), 259-64
CODEN: INNDDK; ISSN: 0167-6997
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The combination of cis-dichlorodiammineplatinum (II) (CisDDPt) + 5-fluorouracil (5-FU) was compared with 2 CisDDPt analogs + 5-FU [iproplatin (CHIP) + 5-FU and carboplatin (CBDCA) + 5-FU] for relative efficacy against advance stage squamous cell lung tumors (LC-12) in Balb/c mice. At equitoxic dosages, the nos. of regressions and cures were similar for the 3 combinations (5-FU/CISDDPt 2/10 PR's, 2/10 CR's, 2/10 cures; 5-FU/CBDCA 1/10PR's, 5/10 CR's, 3/10 cures; 5-FU/CHIP 1/10 PR's, 3/10 CR's, 3/10 cures). The tumor growth delay among the mice not cured was slightly superior in the 5-FU/CisDDPt regimen. All the agents were active singly against this tumor model. Thus, the substitution of CBDCA or CHIP for CisDDPt in a FU regimen did not offer a cytotoxic advantage. Because of different dose limiting toxicities for the platinum compds. the possibility exists that these analogs could be used in drug combinations in substitution for CisDDPt.
CC 1-6 (Pharmacology)

L17 ANSWER 35 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1987:590359 CAPLUS
DOCUMENT NUMBER: 107:190359
TITLE: A-ring substituted estrogens as inhibitors of the MXT transplantable mammary ductal carcinoma
AUTHOR(S): Brooks, S. C.; **Horwitz, J. P.**; Odden, D.; **Corbett, T.**
CORPORATE SOURCE: Sch. Med., Wayne State Univ., Detroit, MI, 48201, USA
SOURCE: Cancer Research (1987), 47(17), 4623-9
CODEN: CNREA8; ISSN: 0008-5472
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A-ring substituted estrogens were examined as growth inhibitors of the hormone dependent MXT murine mammary tumor. Certain of these estrogen analogs inhibited the growth of newly implanted as well as established MXT tumors when administered either by s.c. or i.p. injections or by intubation. These compds. were nontoxic over a broad range of active levels. Amino and nitro groups, introduced at position-4 of estrone 3-Me ether were particularly carcinostatic, a property not shared by 4-bromoestrone 3-Me ether. In addition tumor inhibition was greatly diminished by placing the nitro group at the other ortho position (i.e., C-2). Evidence indicates that the A-ring substituted estrogens may function as growth inhibitors via the estrogen receptor mechanism in the

case of 4-nitro- and 4-aminoestrone. The 3-Me ethers of these compds. also blocked tumor growth, possibly through in vivo dealkylation leading to the free phenolic A-ring substituted estrogens. On the other hand, A-ring substituted 3-deoxyestrogens (particularly 4-nitro- and 4-aminoestratrien-17β-ol), which do not bind to receptor, were also excellent inhibitors of hormone dependent MXT breast tumors and therefore must express their activity by mechanisms other than that mediated by receptor. The A-ring substituted estrogens are unlike tamoxifen and DES which display toxicity at optimum inhibitory doses and are inactive or marginally active in rodent cancer models.

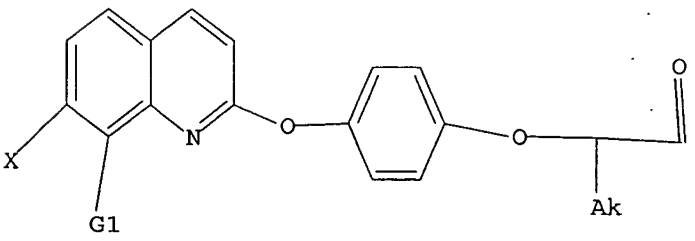
CC 1-3 (Pharmacology)
Section cross-reference(s): 2, 32

L17 ANSWER 36 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1987:113237 CAPLUS
DOCUMENT NUMBER: 106:113237
TITLE: Activity of flavone acetic acid (NSC-347512) against solid tumors of mice
AUTHOR(S): **Corbett, Thomas H.**; Bissery, Marie Christine; Wozniak, Antoinette; Plowman, Jacqueline; **Polin, Lisa**; Tapazoglou, Efstathios; Dieckman, Julia; Valeriote, Frederick
CORPORATE SOURCE: Sch. Med., Wayne State Univ., Detroit, MI, 48201, USA
SOURCE: Investigational New Drugs (1986), 4(3), 207-20
CODEN: INNDDK; ISSN: 0167-6997
DOCUMENT TYPE: Journal
LANGUAGE: English

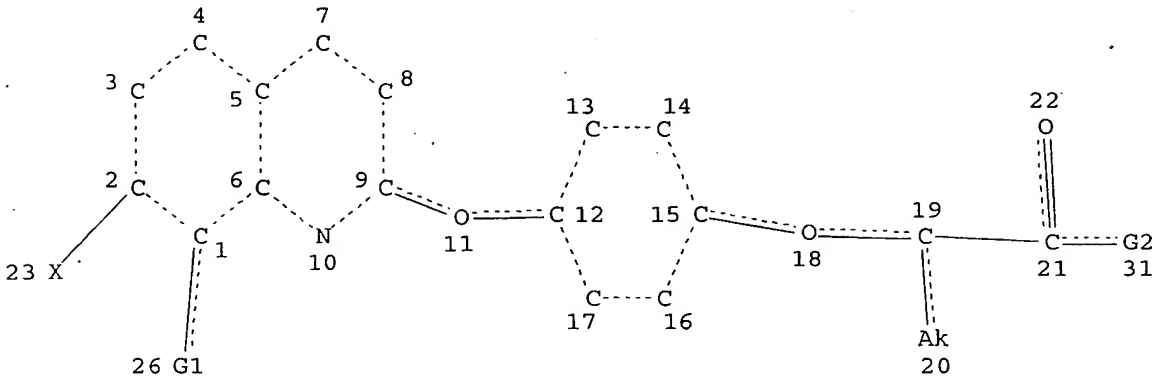
AB NSC 347512 (flavone acetic acid, FAA) [87626-55-9] is a new antitumor agent that has recently entered Phase I clin. trials. In preclin. studies, FAA was broadly active against a variety of transplantable solid tumors of mice (colon, pancreatic ductal adenocarcinomas, mammary adenocarcinoma, M5076 reticulum cell sarcoma, and osteosarcoma). FAA was curative for colon adenocarcinoma and pancreatic ductal adenocarcinoma. FAA was also orally active and stable in solution at 37° for 48 h. FAA was selectively cytotoxic in vitro for solid tumors over leukemias L1210 and P388 (in a soft-agar colony formation assay), thus correlating cellular selectivity in vitro with in vivo antitumor activity. The finding that FAA was active in vitro, established that the agent did not need metabolism (activation) outside the tumor cell. The main drawback of FAA was an unusual 'threshold' behavior in which only a narrow range of doses were active and splitting the dose markedly decreased activity.

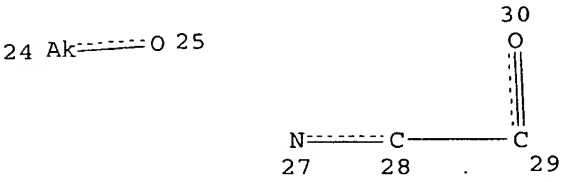
CC 1-6 (Pharmacology)

```
=> file marpat
FILE 'MARPAT' ENTERED AT 16:16:18 ON 11 MAY 2006
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2006 American Chemical Society (ACS)

FILE CONTENT: 1961-PRESENT VOL 144 ISS 19 (20060505/ED)

SOME MARPAT RECORDS ARE DERIVED FROM INPI DATA FOR 1961-1987

MOST RECENT CITATIONS FOR PATENTS FROM MAJOR ISSUING AGENCIES
(COVERAGE TO THESE DATES IS NOT COMPLETE):

US   2006062725 23 MAR 2006
DE 102004042453 02 MAR 2006
EP      1630163 01 MAR 2006
JP   2006054951 23 FEB 2006
WO   2006034632 06 APR 2006
GB      2416167 18 JAN 2006
FR      2875804 31 MAR 2006
RU      2270725 27 FEB 2006
CA      2477020 09 FEB 2006

Expanded G-group definition display now available.

New CAS Information Use Policies, enter HELP USAGETERMS for details.

=> d que l28
L1              STR
```

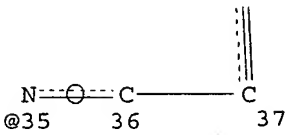

```
G1 H,OH,[@1]

Structure attributes must be viewed using STN Express query preparation.
L18          32 SEA FILE=REGISTRY SSS FUL L1
L19           7 SEA FILE=CAPLUS ABB=ON  PLU=ON  L18
L25             STR
```





H 32 33 O M1 Hy 34

Page 1-A



Page 2-A
VAR G1=32/33/25
VAR G2=34/27/35
NODE ATTRIBUTES:

HCOUNT	IS M1	AT	33
NSPEC	IS R	AT	1
NSPEC	IS R	AT	2
NSPEC	IS R	AT	3
NSPEC	IS R	AT	4
NSPEC	IS R	AT	5
NSPEC	IS R	AT	6
NSPEC	IS R	AT	7
NSPEC	IS R	AT	8
NSPEC	IS R	AT	9
NSPEC	IS R	AT	10
NSPEC	IS C	AT	11
NSPEC	IS R	AT	12
NSPEC	IS R	AT	13
NSPEC	IS R	AT	14
NSPEC	IS R	AT	15
NSPEC	IS R	AT	16
NSPEC	IS R	AT	17

```
NSPEC   IS C      AT  18
NSPEC   IS C      AT  19
NSPEC   IS C      AT  20
NSPEC   IS C      AT  21
NSPEC   IS C      AT  22
NSPEC   IS C      AT  23
NSPEC   IS C      AT  24
NSPEC   IS C      AT  25
NSPEC   IS C      AT  26
NSPEC   IS RC     AT  27
NSPEC   IS RC     AT  28
NSPEC   IS C      AT  29
NSPEC   IS C      AT  30
NSPEC   IS C      AT  31
NSPEC   IS RC     AT  35
NSPEC   IS RC     AT  36
NSPEC   IS C      AT  37
NSPEC   IS C      AT  38
DEFAULT MLEVEL IS ATOM
MLEVEL  IS CLASS  AT  11 18 19 20 21 22 23 24 25 27 28 29 30 32 33 34 35
          36 37 38
GGCAT   IS LOC  AT  20
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  38

STEREO ATTRIBUTES: NONE
L27           5 SEA FILE=MARPAT SSS FUL L25
L28           3 SEA FILE=MARPAT ABB=ON  PLU=ON  L27 NOT L19
```

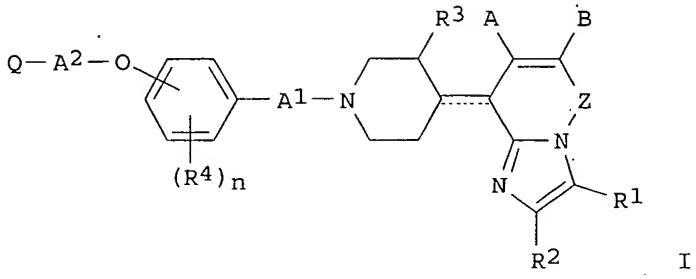
=> d ibib abs qhit l28 tot

L28 ANSWER 1 OF 3 MARPAT COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 127:307385 MARPAT
TITLE: Fused imidazole derivatives as multidrug resistance modulators
INVENTOR(S): Janssens, Frans Eduard; Leenaerts, Joseph Elisabeth; Sommen, Francois Maria; Surleraux, Dominique Louis Nestor Ghislaine
PATENT ASSIGNEE(S): Janssen Pharmaceutica N.V., Belg.; Janssens, Frans Eduard; Leenaerts, Joseph Elisabeth; Sommen, Francois Maria; Surleraux, Dominique Louis Nestor Ghislaine
SOURCE: PCT Int. Appl., 52 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

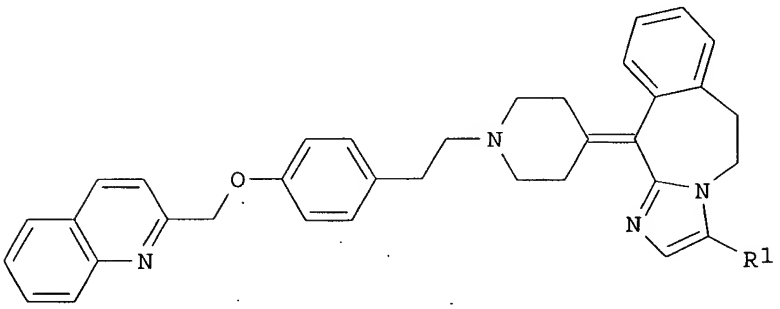
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9734897	A1	19970925	WO 1997-EP1264	19970311
W: AL, AM, AU, BB, BG, BR, CA, CN, CU, CZ, EE, GE, HU, IL, IS, JP, KG, KR, LC, LK, LR, LT, LV, MD, MG, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
TW 527186	B	20030411	TW 1997-86102623	19970305
CA 2237594	AA	19970925	CA 1997-2237594	19970311
AU 9720269	A1	19971010	AU 1997-20269	19970311
AU 709683	B2	19990902		
EP 888352	A1	19990107	EP 1997-908226	19970311
EP 888352	B1	20030528		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, SI, LT, LV, FI, RO				
CN 1211985	A	19990324	CN 1997-192399	19970311
CN 1083453	B	20020424		
BR 9708140	A	19990727	BR 1997-8140	19970311
JP 2000505477	T2	20000509	JP 1997-533121	19970311
JP 3630434	B2	20050316		
JP 2002012594	A2	20020115	JP 2001-167003	19970311
IL 124572	A1	20020310	IL 1997-124572	19970311
EE 3773	B1	20020617	EE 1998-281	19970311
AT 241626	E	20030615	AT 1997-908226	19970311
IL 143998	A1	20030624	IL 1997-143998	19970311
ES 2200159	T3	20040301	ES 1997-908226	19970311
CZ 294060	B6	20040915	CZ 1998-1529	19970311
SK 284434	B6	20050401	SK 1998-662	19970311
ZA 9702351	A	19980918	ZA 1997-2351	19970318
HR 970161	B1	20020630	HR 1997-970161	19970319
NO 9802124	A	19980918	NO 1998-2124	19980511
NO 310659	B1	20010806		
US 6218381	B1	20010417	US 1998-142932	19980917
HK 1015769	A1	20030926	HK 1999-100695	19990220
US 6476018	B1	20021105	US 2001-775524	20010202
IL 143997	A1	20030212	IL 2001-143997	20010626
US 2003087895	A1	20030508	US 2002-187665	20020702

JP 2004067701 A2 20040304
PRIORITY APPLN. INFO.: JP 2003-349802 20031008
EP 1996-200755 19960319
IL 1997-124572 19970311
JP 1997-533121 19970311
WO 1997-EP1264 19970311
US 1998-142932 19980917
US 2001-775524 20010202

GI



I

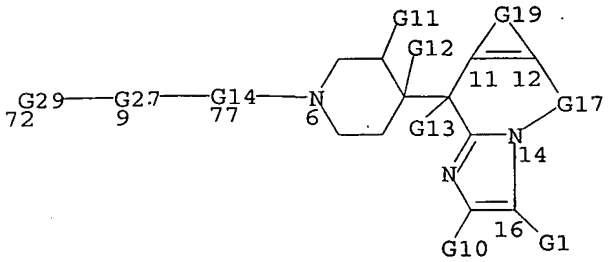


II

AB The invention concerns compds. I and their N-oxide forms, pharmaceutically acceptable addition salts, and stereochem. isomeric forms [wherein the dotted line = optional pi bond; n = 1 or 2; R1 = H, halo, CHO, alkyl (optionally substituted with OH, alkoxy, alkylcarbonyloxy, imidazolyl, thiazolyl or oxazolyl), XCO2R5, XCONR6R7, or XCOR10; X = bond, alkanediyl, or alkenediyl; R5 = H, alkyl, Ar, Het, and alkyl substituted with alkoxy, Ar, or Het; R6, R7 = H or alkyl; R10 = imidazolyl, thiazolyl, or oxazolyl; R2 = H, halo, alkyl, hydroxyalkyl, alkoxycarbonyl, CO2H, CHO, or Ph; R3 = H, alkyl, or alkoxy; R4 = H, halo, alkyl, alkoxy, or haloalkyl; Z = CH2, CH2CH2, CH:CH, CH(OH)CH2, OCH2, COCH2, or C(:NOH)CH2; AB = bivalent radical; A1 = bond, (un)substituted alkanediyl, alkanediyloxyalkanediyl, CO, alkanediylcarbonyl, (un)substituted alkanediyloxy; A2 = bond or alkanediyl; Q = (un)substituted Ph, naphthalenyl, pyridinyl, or quinolinyl; Ar = (un)substituted Ph; Het = (un)substituted furanyl, oxazolyl, or quinolinyl]. Also disclosed are processes for preparing I, formulations comprising them, and their use as medicines, particularly for inhibiting or reversing the effects of multidrug resistance (MDR). I are useful for combating MDR phenomena in both cancers and pathogens. Approx. 100 compds. I were prepared For instance, N-alkylation of 3-chloro-6,11-dihydro-11-(4-piperidinylidene)-5H-imidazo[2,1-b][3]benzazepine with 4-(2-quinolinylmethoxy)benzeneethanol mesylate ester

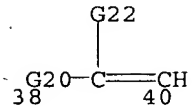
(prepns. given) in refluxing EtOH in the presence of NaHCO3 gave 73% title compound II [R1 = Cl]. In a test against the adriamycin-resistant murine leukemia cell line P388/ADR in mice, adriamycin at 1.25 mg/kg plus II [R1 = CO2Me] at 0.63-20 mg/kg gave a 14-23% increase in mean survival time over adriamycin alone.

MSTR 1

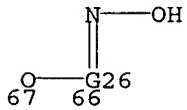


G14 = 8-9 7-6

G17 = CH2
G19 = 38-11 40-12



G20 = O
G23 = 67-8 66-6



G26 = carbon chain <containing 1-6 C, saturated>
(opt. substd. by OH)
G27 = O
G29 = quinolinyl (opt. substd. by (1-2) G30)
G30 = F
G32 = phenylene (opt. substd. by (1-2) G15)
Derivative: and N-oxide forms and pharmaceutically acceptable salts
Patent location: claim 1
Note: substitution is restricted
Stereochemistry: or stereochemically isomeric forms

L28 ANSWER 2 OF 3 MARPAT COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 110:135096 MARPAT

TITLE: Preparation of quinoline containing sulfonylcarboxamides as allergy and inflammation inhibitors

INVENTOR(S): Kreft, Anthony Frank, III; Musser, John Henry; Kubrak, Dennis Martin

PATENT ASSIGNEE(S): USA

SOURCE: Brit. UK Pat. Appl., 33 pp.
CODEN: BAXXDU

DOCUMENT TYPE: Patent

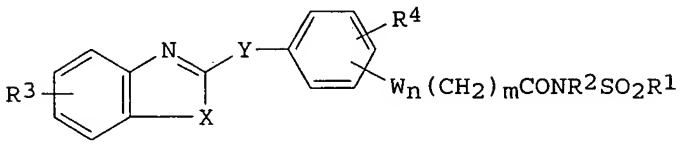
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

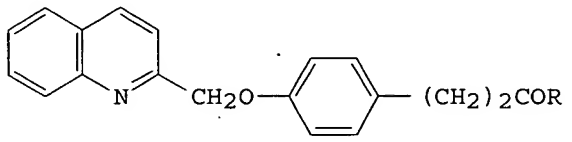
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
GB 2202223	A1	19880921	GB 1988-6373	19880330
GB 2202223	B2	19910529		
WO 8806886	A2	19880922	WO 1988-US767	19880316
WO 8806886	A3	19890112		
W: AU, JP, KR				
RW: AT, BE, CH, DE, FR, GB, IT, LU, NL, SE				
AU 8815497	A1	19881010	AU 1988-15497	19880316
EP 309541	A1	19890405	EP 1988-903531	19880316
EP 309541	B1	19920102		
R: AT, BE, CH, DE, FR, IT, LI, LU, NL, SE				
JP 01502755	T2	19890921	JP 1988-503171	19880316
AT 70976	E	19920115	AT 1988-903531	19880316
CA 1314048	A1	19930302	CA 1988-561795	19880317
PRIORITY APPLN. INFO.:			US 1987-27452	19870318
			EP 1988-903531	19880316
			WO 1988-US767	19880316

GI



I

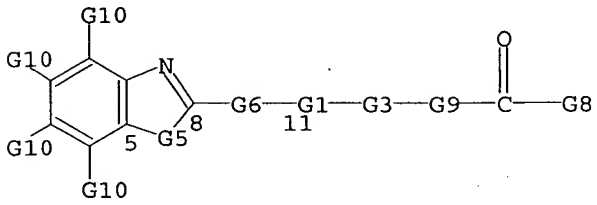


II

AB Title compds. I (W = O, S, NR2, CH2; X = O, S, NR2, CH:CH, CH:N, N:CH; Y = CH2O, CH2S, CH2NR2, O, S, NR2, CONR2, CHR2CHR2, CR2:CR2; R1 = alkyl, perfluoroalkyl, (R5-substituted Ph; R2 = H, alkyl; R3,R4,R5 = H, alkyl, NO2, CF3, Me, halo, alkoxy, alkoxycarbonyl, alkanoyloxy; n = 0, 1; m = 0-10) are prepared A solution of p-HOC6H(CH2)2CO2H in MeOH was successively treated with MeONa and with 2-chloromethylquinoline in DMF at room temperature to give 31% a propionate II (R = quinoline-2-methoxy) which in THF was refluxed with 1N NaOH to give II (R = OH), and the latter in THF was treated with p-MeC6H4SO2NH2 in the presence of 1,1-carbonylimidazole to

afford 31% II (R = p-MeC6H4SO2NH)(III). III at 25 mg/kg intraduodenally showed 97% inhibition of leukotrienes-induced bronchospasm in guinea pigs.

MSTR 2A



G1 = phenylene (opt. substd. by (1) G2)
G3 = O
G5 = CH=CH
G6 = O
G8 = imidazolyl
G9 = alkylene <containing 1-10 C, unbranched>
G10 = F
Patent location: claim 12

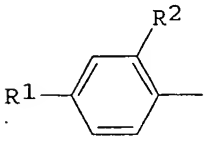
L28 ANSWER 3 OF 3 MARPAT COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 97:34711 MARPAT
TITLE: Enhancement of carbohydrate deposition in plants by substituted phenoxyalkanoic acid and cyclohexanedione derivatives
INVENTOR(S): Bieringer, Hermann; Buerstell, Helmut; Handte, Reinhard; Koecher, Helmut; Schulze, Ernst Friedrich
PATENT ASSIGNEE(S): Hoechst A.-G., Fed. Rep. Ger.
SOURCE: Eur. Pat. Appl., 21 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 47972	A2	19820324	EP 1981-107070	19810909
EP 47972	A3	19820616		
EP 47972	B1	19851030		
R: DE, FR, IT, SE				
DE 3034845	A1	19820506	DE 1980-3034845	19800916
AU 8175247	A1	19820325	AU 1981-75247	19810915
AU 547196	B2	19851010		
BR 8105902	A	19820608	BR 1981-5902	19810915
ZA 8106386	A	19820929	ZA 1981-6386	19810915
HU 30506	O	19840328	HU 1981-2663	19810915
CA 1169262	A1	19840619	CA 1981-385908	19810915
US 4564381	A	19860114	US 1983-540093	19831007
PRIORITY APPLN. INFO.:			DE 1980-3034845	19800916
			US 1981-302189	19810914

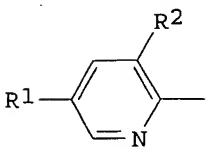
GI

I

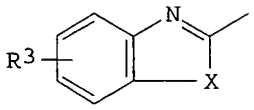
II



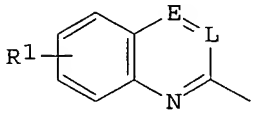
III



IV



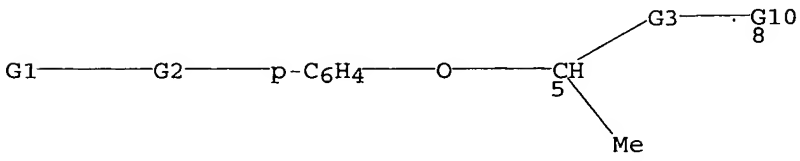
V



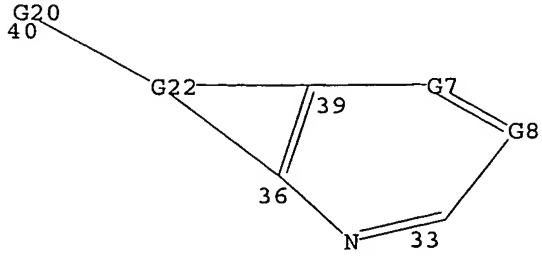
VI

AB The carbohydrate content of plants was increased by I and II (Z = III-VI; Y = CH2, NH, etc.; A = CH2CH2, CH:CH, etc.; B = CO2R4, COSR5, CONR6R7, or CONR8NR9R10; X = O or S; E = CH, N, or NO; L = CH or N; R' = halo, CF3, CF2H, OCF3, CN, or NO2; R2 = H, F, Cl, CF3, CN, or NO2; R3 = H, F, Cl, Br, or CF3; R4 = H, alkyl, aryl, etc.; R5 = C1-6 alkyl, C3-6 alkenyl, benzyl, Ph, CHR8CO2R11, etc.; R6 = H or C1-4 alkyl; R7 = H, C1-10 alkyl, Ph, etc.; NR6R7 = heterocyclic radical; R8 = H or Me; R9 and R10 = H, C1-4 alkyl, etc.; R11 = H, C1-4 alkyl, etc.; R12 = C1-4 alkyl, allyl, or Ph; R13 = H, C1-4 alkyl, or Ph; R14 = H, C1-4 alkoxycarbonyl, or C1-4 alkyl; R15 = C1-4 alkyl etc.). Thus, in a greenhouse experiment, dewlap application of 2 mg Et D-(+)-2-[4-(6-chloro-2-benzoxazolyloxy)phenoxy]propanoate [71283-80-2] increased the sugar content of sugarcane at harvest by 84%.

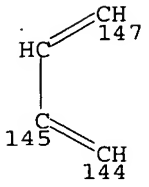
MSTR 1



G1 = 33

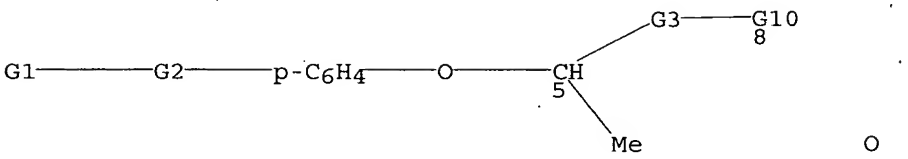


G2 = O
G3 = C(O)
G7 = CH
G8 = CH
G10 = pyrrolidino
G20 = halo
G22 = 144-36 145-40 147-39

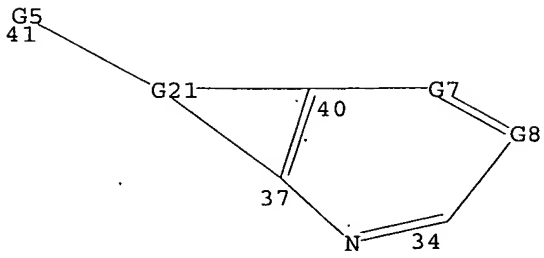


Patent location: claims
Note: record may include structures from disclosure

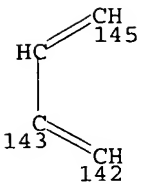
MSTR 3



G1 = 34



G2 = O
G3 = C(O)
G5 = halo
G7 = CH
G8 = CH
G10 = pyrrolidino
G21 = 142-37 143-41 145-40



Patent location: claims
Note: record may include structures from disclosure